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NEURALE NETZWERKE DER SELBST- UND FREMD-REPRÄSENTATION UND DEREN INTEGRITÄT BEI SCHIZOPHRENIE

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Abkürzungsverzeichnis

ANG	Angulärer Gyrus
ASS	Autismus-Spektrums-Störung
BOLD	Blood oxygen level dependent
CONTR	gesunde Kontrollprobanden
DLPFC	dorsolateraler prefrontaler Kortex
fMRT	funktionelle Magnetresonanz-Tomografie
IFG	inferiorer frontaler Gyrus
IPL	inferiorer parietaler Lobus
LNG	Lingualer Gyrus
mPFC	medialer prefrontaler Kortex
MNS	mirror neuron system, Spiegelneuronensystem
PPI	psychophysiologische Interaktion
PREC/PCC	Precuneus / posteriorer cingulärer Cortex
pSTS	posteriorer Sulcus temporalis superior
SCHIZ	Patienten mit Schizophrenie
TPJ	Temporoparietaler Übergang
ToM	Theory of Mind

Diese Doktorarbeit besteht aus drei Manuskripten (Studie 1-3). Zum Zeitpunkt der Einreichung der Dissertation war Manuskript #1 bereits zu Veröffentlichung akzeptiert und zwei weitere befanden sich seit Juli 2013 unter Begutachtung bei internationalen peer-review Zeitschriften.

Abstract

Social cognition is a key function of human beings. Successfully taking part in social interactions is of great importance for survival. Hence, we have a need for constant screening of social contexts and meaning as well as for accurately attributing the agency of observed actions. Therefore, our brain should be well adapted to these processes. However, impaired social functioning is a core characteristic in schizophrenia (Frith, 1992). In the context of this thesis, three functional magnetic resonance imaging (fMRI) studies were performed investigating the neural processes underlying social cognition abilities in the brain of patients with schizophrenia, as well as in the non-pathologic brain. We focused on three particular social abilities, namely (1) perception of cooperation (Study #1), (2) perception of self-generated and observed actions (Study #2), and (3) inferring agency of observed actions (Study #3).

Until now cooperation is a form of social interaction that has received little attention in the research on schizophrenia – even though it is the very basis of social existence and although it is known that patients show altered cooperation behavior (e.g., Wischniewski et al., 2009). Additionally, patients with paranoid schizophrenia suffer from persecutory delusions, accompanied by feelings of being watched or followed (M. Startup & S. Startup, 2005) caused by false inferences regarding the intentions of others (Frith & Frith, 1999). To date, more empirical research is needed to further investigate the possible relation between social interaction deficits and delusions (Freeman, 2007). For this purpose, we constructed an fMRI paradigm: participants watched video stimuli in which two actors manipulate objects together – or as in the control condition – one actor manipulates the object alone. We studied a possible relation of brain activity in response to the stimuli and psychopathology (Study #1).

Additionally, social cognition deficits are often explained by alterations of the observation-execution matching system i.e., the mirror neuron system (MNS). This system is activated when subjects view or perform grasping movements (e.g., Iacoboni et al., 2005). Surprisingly, just a few studies focus on the functionality of this system in schizophrenia. A simple task was used to probe the integrity of the MNS: participants observed an actor while grasping an object and periodically performed a similar action in the scanner (Study #2). Besides evaluating activation differences between groups, connectivity analyses were performed.

If self and other actions are comparably processed within the MNS, there is a need for a control mechanism that still enables an accurate distinction between self and non-self for agency attributions (David et al., 2008; Leube et al., 2012). Patients with schizophrenia often suffer from delusions of influence (passivity phenomena, ego-disturbances), which suggests that their sense of self is disturbed. It is assumed that a failure of the efference copy mechanism, which compares efferent with reafferent signals and attenuates the sensory

consequences of self-produced movements, causes passivity phenomena (e.g., Blakemore et al., 2000; Ford & Mathalon, 2004). To test this hypothesis, participants performed both intentional and unintentional continuous hand-movements. We periodically manipulated visual feedback of their action by introducing a temporal delay to create a sensory-motor discrepancy – simulating "non-self" feedback (Study #3).

We have shown in Study #1 that the network for perception of cooperative and non-cooperative behavior is altered in a mirror-inverted way in paranoid schizophrenia. More precisely, in schizophrenic patients parts of the cooperation-network showed attenuation in response to the cooperative context, but were significantly increased in the non-cooperative context compared to controls. Furthermore, the latter finding was associated with persecutory delusions in patients. Showing this pattern of results, we provide novel experimental evidence for the idea of an overactivated Theory of mind (ToM) network in patients, which might reflect overmentalizing (e.g., Abu-Akel & Bailey, 2000). This could be attributed to ambiguous perception of the non-cooperative scenes resulting from a constantly hyperactive intention detector (e.g., Walter et al., 2009) and the patients' abnormal threat perception (Bentall & Kaney, 1989; Fear et al., 1996). Moreover, results from Study #1 support the assumption that the ToM network plays an important role in the formation of delusions.

The findings of Study #2 suggest that a broader MNS dysconnectivity may be responsible for the social deficit in schizophrenia that reduces social functioning because it might disturb an essential sensory feedback exchange within the MNS. In Study #2, it is discussed that this newly observed MNS dysconnectivity might be a major contributor to social cognitive aberrances in schizophrenia - e.g., imitation, mentalizing, and empathizing deficits, as well as attributional style. Reduction of these abilities results in abnormal social functioning in schizophrenia (Fett et al., 2011).

In Study #3 we identified the inferior frontal gyrus (IFG) as a potential candidate for a control entity that enables a distinction between self and non-self within the MNS with shared neural representations for "self" and "other". However, in patients the sensory mismatch detection was altered, suggesting that the IFG is the neural correlate of the failure of the efference mechanism in schizophrenia. More specifically, due to dysconnectivity of the IFG to other parts of the mismatch network, signal exchange between perceptual and motor areas (which is necessary for the efference mechanism) seems to be affected. Moreover, alterations in this network were related to passivity symptom-ratings. This defective network might cause self-monitoring deficits in patients, which contributes to clinical core symptoms of schizophrenia i.e. the emergence of disorders of the self (see Farrer & Franck, 2007).

Zusammenfassung

Soziale Kognition ist eine Schlüsselkompetenz menschlicher Individuen. Die erfolgreiche Teilnahme an sozialen Interaktionen innerhalb unserer Gesellschaft ist für das Überleben unerlässlich. Daher bedarf es eines kontinuierlichen Screenings des sozialen Kontexts – inklusive der korrekten Zuordnung von Intentionen oder Urheberschaft einer Handlung. An diese Prozesse muss unser Gehirn bestens angepasst sein. Dies ist bei Patienten mit Schizophrenie nicht der Fall – gestörte soziale Kognitionsfähigkeiten gehören bei dieser Erkrankung zur Kernsymptomatik (Frith, 1992). In der vorliegenden Dissertation wurden die neuralen Prozesse im Gehirn von Patienten mit Schizophrenie sowie im nicht-pathologischen Gehirn untersucht, die Teilaspekten der sozialen Kognitions-Fähigkeiten zugrunde liegen. Dazu wurden drei funktionelle Magnetresonanz-Tomographie (fMRT) Studien durchgeführt, die sich im Speziellen mit (1) der Wahrnehmung von Kooperation (Studie #1), (2) der Wahrnehmung eigener sowie fremder Handlungen (Studie #2) und (3) der Unterscheidung eigener Handlungen von Handlungen anderer (Studie #3) beschäftigen.

Die soziale Kognition innerhalb der Schizophrenie-Forschung ist eine oft bemühte Thematik. Allerdings wurde die Wahrnehmung von Kooperation als Form der sozialen Interaktion nur sehr selten untersucht – obwohl es sich dabei um eine der Grundlagen sozialer Existenz handelt. Zusätzlich ist bekannt, dass Betroffene ein verändertes Kooperationsverhalten zeigen (z. B. Wischniewski et al., 2009). Ferner leiden paranoid-schizophrene Patienten unter Verfolgungswahn, der sich in Gefühlen äußert, beobachtet oder verfolgt zu werden (M. Startup & S. Startup, 2005). Es wird angenommen, dass sie aufgrund falschen Schlussfolgerns hinsichtlich der Intentionen anderer entstehen (C.D. Frith & U. Frith, 1999). Eingehende empirische Forschung ist nötig, um einen möglichen Zusammenhang zwischen defizitärer Wahrnehmung sozialer Interaktion und Wahnsymptomatik zu untersuchen (Freeman, 2007). Im Rahmen dieser Doktorarbeit wurde dazu ein fMRT Paradigma entwickelt, bei dem Schizophreniepatienten und parallelisierte Kontrollprobanden Videos beobachteten, bei denen zwei Darsteller kooperativ bzw. – in der Kontrollbedingung – alleine (eine Person manipuliert, die andere Person beobachtet) Objekte manipulieren. Zusätzlich wurde der Zusammenhang der individuellen Ausprägung von Verfolgungswahn mit der Gehirnaktivierung als Folge der Beobachtung der Stimulusvideos untersucht (Studie #1).

Bei Patienten mit Autismus oder Schizophrenie werden soziale Kognitions-Defizite oft mit einer Störung des Spiegelneuronensystems (mirror neuron system, MNS) erklärt. Dieses Netzwerk ist gleichermaßen aktiviert, wenn Handlungen beobachtet sowie selbst ausgeführt werden (z. B. Iacoboni et al., 2005). Anders als bei Autismus beschäftigten sich bisher Wissenschaftler/innen nicht explizit mit der Funktionalität dieses Systems bei schizophrenen Patienten. Ein einfaches fMRT-Paradigma ermöglichte die Untersuchung dieses Sachverhaltes: Abwechselnd beobachteten die Versuchspersonen im MRT Videos,

in denen ein Darsteller nach einem Objekt griff und wiederholten im Anschluss entsprechend selber die Greifbewegung nach diesem Objekt (Studie #2). Neben der Untersuchung von Aktivierungsunterschieden zwischen Gesunden und Schizophreniepatienten, wurden Konnektivitätsanalysen durchgeführt, um die Integrität des zugrundeliegenden Netzwerkes zu testen.

Wenn „selbst" und „fremd" im MNS gleichermaßen abgebildet werden, bedarf es eines Kontrollsystems, das zwischen beidem unterscheiden kann, um die erfolgreiche Zuordnung von Urheberschaft zu gewährleisten (David et al., 2008; Leube et al., 2012). Bei Patienten mit Schizophrenie gelingt diese Zuordnung nicht immer fehlerfrei. Infolge dessen leiden sie unter Beeinflussungswahn (Ich-Störung, Passivitätsphänomene). Es wird angenommen, das eine Störung des Efferenzkopie-Mechanismus, der motorische Handlungspläne mit sensorischen Handlungskonsequenzen auf neuraler Ebene vergleicht und dadurch die sensorischen Konsequenzen selbstproduzierter Handlungen in der Wahrnehmung abschwächt, diese Passivitätsphänomene hervorruft (z. B. Blakemore et al., 2000; Ford & Mathalon, 2004). Um sich der Funktionsweise dieses Prozesses anzunähern, wurde in der vorliegenden Arbeit die Gehirnaktivität in Folge kontinuierlicher Greifbewegungen untersucht. Abwechselnd wurde das visuelle Feedback dieser Bewegungen manipuliert, indem eine zeitliche Verzögerung eingeführt wurde. Dies führte zu einer Diskrepanz zwischen motorischen Handlungsplänen und den wahrgenommenen sensorischen Handlungskonsequenzen und simulierte damit eine „nicht-selbst" ausgeführte Handlung (Studie #3).

In Studie #1 konnte gezeigt werden, dass sich das Aktivierungsmuster des Netzwerks für die Wahrnehmung kooperativen und nicht-kooperativen Verhaltens bei Patienten mit Schizophrenie genau entgegengesetzt zu gesunden Probanden darstellte. Teile des Kooperations-Netzwerks von Patienten zeigten geringere Aktivität im kooperativen Kontext und signifikant stärkere Aktivierung während Videoszenen ohne Kooperation verglichen mit Probanden. Interessanterweise stand diese Hyperaktivierung im Zusammenhang mit der individuellen Ausprägung des Verfolgungswahns. Mit diesen Ergebnissen können wir neue experimentelle Belege für die Theorie eines überaktivierten Mentalisierungs-Netzwerks und Hypermentalisierungs-Tendenzen (z. B. Abu-Akel & Bailey, 2000) bei Patienten mit Schizophrenie liefern. Im vorliegenden Fall ist dieses Ergebnis am ehesten auf eine mehrdeutige wahnhafte Wahrnehmung der nicht-kooperativen Szenen zurückzuführen, basierend auf einem hyperaktiven Intentions-Detektor (z. B. Walter et al., 2009) sowie verstärkter Bedrohungswahrnehmung (Bentall & Kaney, 1989; Fear et al., 1996). Darüber hinaus stützt diese Studie die Annahme, dass das Mentalisierungs-Netzwerk eine wichtige Rolle bei der Entstehung von Wahn einnimmt.

Die Ergebnisse von Studie #2 legen nahe, dass eine ausgedehnte Dyskonnektivität des MNS für soziale Defizite bei Patienten mit Schizophrenie verantwortlich ist. Solche Defizite

könnten auf einem gestörten Feedback-Austausch innerhalb dieses Systems basieren. In Studie #2 wird diskutiert, ob die neue Erkenntnis einer der Hauptgründe für die verminderte soziale Funktionsfähigkeit von Patienten in den Bereichen Imitation, Mentalisierung, Empathie und voreiliges Schlussfolgern ist.

In der dritten Studie (Studie #3) konnte der inferiore frontale Gyrus (IFG) als potentieller Kandidat für einen Kontrollmechanismus innerhalb des MNS identifiziert werden. Bei gesunden Probanden gewährleistet er durch seine Antwortcharakteristik eine Unterscheidung zwischen „selbst“ und „nicht-selbst“, obwohl im MNS üblicherweise „selbst“ und „fremd“ gleichermaßen abgebildet werden. Bei Patienten war die Aktivität in diesem System allerdings in einer Art verändert, die nahelegt, dass der IFG das neurale Korrelat eines defizitären Efferenzkopie-Mechanismus darstellt. Neben einer veränderten Antwortcharakteristik war die funktionelle Konnektivität zu anderen Teilen des „Self-Monitoring“-Netzwerks vermindert, wodurch der essentielle Austausch von Abgleichssignalen (motorische Handlungspläne, sensorisches Feedback etc.) zwischen motorischen und sensorischen Arealen im Gehirn beeinträchtigt sein könnte. Ein Zusammenhang zwischen den Veränderungen innerhalb dieses Netzwerks mit der Ausprägung der Ich-Störungen konnte hier gezeigt werden. Zusammenfassend könnten diese Veränderungen zu den „Self-Monitoring“-Defiziten führen, die zur Kernsymptomatik der Schizophrenie beitragen (für ein Review siehe Farrer & Franck, 2007).

Kapitel 1

Einleitung

1.1. Soziale Kognition und deren Beeinträchtigung in der Schizophrenie

Das Leben in unserer stark sozialisierten Gesellschaft erfordert eine ständige Wahrnehmung und Verarbeitung von sozialen Informationen und eine permanente Anpassung des eigenen Verhaltens in sozialen Kontexten. Das multidimensionale Konstrukt der Sozialen Kognition fasst die zugrunde liegenden kognitiven, emotionalen und behavioralen Prozesse zusammen, mit denen der Mensch sich und andere im sozialen Umfeld versteht (Ostrom, 1984; Adolphs, 2001). Zur Sozialen Kognition werden auch ganz grundlegende Vorgänge gezählt, wie etwa die Wahrnehmung von Handlungen und deren kausale Zuordnungen zu sich selbst oder zu anderen Personen. Es ist offenkundig, dass die fehlerfreie Verarbeitung solcher sozialen Informationen von hoher Bedeutung für eine erfolgreiche Teilnahme an sozialen Interaktionen ist.

Bei Menschen mit Schizophrenie sind Wissenschaftler/Innen sich einig, dass verschiedene Domänen der sozialen Kognition beeinträchtigt sind (z. B. Green et al., 2012). Von primärem Forschungsinteresse sind vor allem die verminderten Fähigkeiten sich und anderen mentale Zustände zuzuschreiben (Theory of Mind, ToM; für Übersichtsartikel siehe Bora et al., 2009; Sprong et al., 2007), Emotionen anderer zu verstehen und zu verarbeiten (z. B. Li et al., 2010), die fehlerhafte soziale Wahrnehmung von z. B. Rollen und Kontexten sowie veränderte kausale Attribution bei der Erklärung sozialer Events (z. B. Green & Horan, 2010; Green et al., 2012). Diese sozialen Kognitionsdefizite bleiben über den Krankheitsverlauf hinweg stabil (Bertrand et al., 2007) und haben einen sehr starken, negativen Einfluss auf das soziale Funktionsniveau der Patienten (Fett et al., 2011). Die Stärke der Ausprägungen einiger dieser sozialen Defizite lassen sich an folgendem Erlebnisbericht eines Patienten mit einer schizophrenen Störung, der Teilnehmer in einer der Studien war, veranschaulichen:

> *„Ich war im Bus auf dem Weg nach Bad Endbach, da beschimpfte mich der Busfahrer unvermittelt und schmiss mich irgendwo in verlassener Gegend aus dem Bus. Nach einigen Stunden kam ein weiterer Bus. Die Türen gingen auf und es standen plötzlich drei, mit Maschinenpistolen bewaffnete Männer vor mir. Sie zwangen mich einzusteigen und brachten mich gegen meinen Willen hierher. Sie verschwanden wieder, aber ich wurde hier überall überwacht. Ich konnte nicht fliehen. Ich konnte mich einfach nicht bewegen. Irgendeine Macht hielt mich hier."*
>
> *(Patient mit paranoider Schizophrenie, 22 Jahre alt)*

Falls dieser wahnhafte Bericht einen wahren Kern haben sollte, so lassen sich an ihm einige Kerncharakteristiken der paranoiden Schizophrenie erläutern. Man könnte sich vorstellen, dass der Busfahrer den Patienten darauf hingewiesen hat, dass es sich um die Endstation handele und er aussteigen solle, während der Patient mit insuffizienten ToM-Fähigkeiten die Intentionen des Busfahrers als unvermittelte Beschimpfung und Rausschmiss missinterpretiert haben könnte. Die Entführung durch bewaffnete Männer und die angedeutete Überwachung spiegeln sehr gut das Symptom des Verfolgungswahns wieder, unter dem ca. 80% bis 90% der schizophrenen Patienten leiden (Brakoulias & Starcevic, 2008; Moutoussis et al., 2007). Der berichtete Wille zu fliehen, sich aber nicht bewegen zu können weil jemand anderes Macht über ihn hat, kann als Ich-Störung gedeutet werden. Dieses Fremdbeeinflussungserleben entsteht, wenn Patienten die Urheberschaft von Handlungen, Gedanken und Gefühlen nicht eindeutig einem Autor – sich oder einer anderen Person – zuordnen können (Farrer & Franck, 2007). Ich-Störungen stehen im starken Zusammenhang mit anderen sozial-kognitiven Fähigkeiten (Schimansky et al., 2012) und lassen sich, wie auch der Verfolgungswahn, zu einem paranoid-halluzinatorischen Symptomcluster zusammenfassen (Knoblich et al., 2004; Läge et al., 2012).

Die genannten Symptome resultieren weitestgehend aus fehlerhaften Interpretationen sozialer Informationen und haben erhebliche soziale Beeinträchtigungen zur Folge. Aus ihnen folgen Kommunikationsprobleme, die in vielen Fällen zur Stigmatisierung und Ausgrenzung führen, die wiederum zur weiteren Verschlechterung des sozialen Funktionsniveaus beitragen (Muñoz et al., 2011). Die empfundene Belastung der Betroffenen, die Spezifität der Symptomatik, das hohe Lebenszeitrisiko der Schizophrenie (ca. 0,5 %; Saha et al., 2008) und die bisher noch unzulänglichen Therapieprogramme für die Verbesserung des sozialen Funktionsniveaus (Lindenmayer et al., 2013), machen eine eingehende neurobiologische Untersuchung der zugrunde liegenden Mechanismen erforderlich, um die Therapieentwicklung spezifisch in der sozialen Domäne zu unterstützen.

Im Rahmen der vorliegenden Dissertation sollten neuronale Netzwerke von schizophrenen und gesunden Teilnehmern, die an den angesprochenen Teilaspekten sozialer Kognition beteiligt sind, mittels funktioneller Magnetresonanz-Tomographie (fMRT) untersucht werden. In Anlehnung an die oben skizzierte Missinterpretation von Intentionen und fehlerhafte Zuordnung der Urheberschaft galt das besondere Interesse der Arbeit, der Fragestellung, wie und wo im Gehirn eigene und fremde Handlungen verarbeitet und unterschieden werden. Ein besonderes Augenmerk wurde darauf gelegt, welche Netzwerke bei Schizophreniepatienten beeinträchtigt sind.

Diese Arbeit gliedert sich in einen theoretischen Teil, in dem die bestehende Literatur zusammengefasst (Kapitel 1.2. - 1.3.), ungelöste Probleme herausgestellt sowie die Ziele der Dissertation (Kapitel 1.5.) und die angewendeten Methoden (Kapitel 1.4.) beschrieben wer-

den. Des Weiteren soll der Zusammenhang zwischen den Studien, die dieser Dissertation zugrunde liegen, hervorgehoben werden. Im Anschluss wird noch einmal gezielt auf die Ergebnisse der einzelnen Studien eingegangen (Kapitel 2.-4.). Abschließend werden die Ergebnisse und deren Implikationen integriert und im Zusammenhang diskutiert (Kapitel 5.).

1.2. Neurale Grundlagen der Wahrnehmung von Handlungen im sozialen Kontext

Für erfolgreiche soziale Interaktionen ist es von herausragender Bedeutung auf beobachtete Handlungen des Gegenübers adäquat reagieren zu können. Hierzu muss zuerst dessen Bewegungen wahrgenommen, die Ziele seiner Handlung identifiziert und die mentalen Zustände der Person evaluiert werden. Es gibt zwei Netzwerke im menschlichen Gehirn, die vornehmlich mit diesen Prozessen in Zusammenhang gebracht werden – das ToM-Netzwerk und das Spiegelneuronensystem (mirror neuron system, MNS). Beide Netzwerke sind anatomisch und funktional zu unterscheiden, arbeiten aber komplementär (de Lange et al., 2008; Hesse et al., 2009; Keysers & Gazzola, 2007; Spunt & Liebermann, 2012) und interagieren (Van Overvalle & Baetens, 2009).

Dem ToM-Netzwerk werden vor allem der mediale präfrontale Kortex (mPFC), der temporo-parietale Übergang (TPJ), der Sulcus temporalis superior (STS) (Amodio & Frith, 2006; Saxe, 2006), der Precuneus und der posteriore cinguläre Kortex (PREC/PCC) des menschlichen Gehirns zugeordnet (Ciaramidaro et al., 2007; U. Frith & C.D. Frith, 2003; Saxe, 2006). Entsprechende Areale wurden in Zusammenhang mit der Vorhersage und der Erklärung des Verhaltens anderer auf der Basis des Verständnisses ihrer Intentionen gebracht. Diese Aufgaben – auch Mentalisierungsfähigkeiten genannt – werden üblicherweise durch explizites Zuordnen von Intentionen zu Akteuren in Cartoongeschichten (z. B. Brunet et al., 2000), in False-Belief-Geschichten (z. B. Frith & Corcoran, 1996), aber auch zu bewegten geometrischen Formen (z. B. Castelli et al., 2000) untersucht.

Es gibt verschiedene Theorien, wie solche Intentionszuordnungen gelingen, beispielsweise die Simulationstheorie des ToM. Diese besagt, dass die Handlungen anderer über den Abruf von Wissen über sich selbst verarbeitet werden und gesammelte eigene Erfahrungen bei der Beurteilung von mentalen Zuständen behilflich sind (Platek et al., 2004; Apperly, 2008). Diesem Prozess der inneren Nachahmung könnte die Funktionsweise des MNS gerecht werden. Dieses Netzwerk besteht aus Neuronen, die aktiv sind, wenn eine motorische Handlung ausgeführt wird – sowie während der Beobachtung einer anderen Person, die selbige ausführt. Diese Neurone wurden erstmals im Kortex von Affen entdeckt (Gallese et al., 1996; Rizzolatti et al., 1996). Bildgebende Studien lieferten im Laufe des letzten Jahrzehnts jedoch überzeugende Hinweise für ein homologes humanes MNS (z. B. Binkofski et al., 2000; Buccino et al., 2001; Iacoboni et al., 1999). Auch gibt es seit Kurzem Evidenz dafür

aus elektrophysiologischen Studien am menschlichen Kortex (Mukamel et al., 2010). Das MNS wird als mögliches neuronales Substrat für die „Common Coding"-Theorie betrachtet (Otte et al., 2011), wobei unter „Common Coding" die gemeinsame Verarbeitung von Handlungsbeobachtung und -steuerung in denselben Gehirnstrukturen verstanden wird. Dieses Netzwerk könnte ein auf Motorik basiertes Verstehen der Handlungsziele anderer ermöglichen, indem die intuitiv beobachtete Handlung automatisch mit der motorischen Handlung mit gleichem Ziel im Repertoire des Beobachters abgeglichen wird und daraufhin die dynamische Anpassung des eigenen Verhalten gewährleistet (Rizzolatti & Sinigaglia, 2010). Dieser Spiegelmechanismus könnte in sozialen Interaktionen beispielsweise der Imitation (Rizzolatti & Craighero, 2004), der Vorhersage von Intentionen beobachteter Handlungen (Kilner et al., 2007; Rizzolatti & Sinigaglia, 2010) und auch der Emotionserkennung (Enticott et al., 2008a) dienen. Zu den Gehirnregionen, die in Bildgebungs-Studien dann reliabel aktiviert sind, wenn eigene Handlungen ausgeführt und wenn Handlungen anderer beobachtet werden – also Spiegeleigenschaften aufweisen – gehören der inferiore frontale Gyrus (IFG), der inferiore Parietallappen (IPL) und der posteriore STS (pSTS; siehe Reviews in Rizzolatti & Graighero, 2004; Dinstein et al., 2007; Metaanalyse: Van Overwalle & Baetens, 2009). Darüber hinaus konnte kürzlich mittels transkranialer magnetischer Stimulation ein kausaler Zusammenhang für den IFG gezeigt werden: Die gleiche Population visuo-motorischer Neurone wurde bei der Beobachtung und Ausführung einer Handlung rekrutiert (Cattaneo et al., 2011). Die Autoren lieferten somit einen direkten Hinweis für Spiegeleigenschaften dieser Neuronenpopulation im IFG und zeigten durch ihre Studie, dass dieser Mechanismus eine Rolle beim Verständnis der beobachteten Handlung spielen könnte.

In einigen Studien konnte bereits demonstriert werden, dass sowohl das ToM-Netzwerk als auch das MNS bei non-verbaler Kommunikation durch Gesten gleichzeitig aktiv sind (z. B. Schippers et al., 2009; Liew et al., 2011). In der vorliegenden Arbeit wurde untersucht, ob beide Netzwerke auch eine Rolle bei der Wahrnehmung von realistischem, kooperativen Verhalten (bzw. sozialer Interaktion) spielen (Studie #1, Kapitel 2.). Des Weiteren sollte analysiert werden, welche Bereiche dieser Netzwerke bei Patienten bei Beobachtung von kooperativen Verhalten dysfunktional sind. Es gibt bereits viele Hinweise dafür, dass das ToM-Netzwerk bei schizophrenen Patienten Auffälligkeiten aufweist (Bora et al., 2009; Brüne, 2005; Corcoran et al., 1995; Harrington et al., 2005b; Sprong et al., 2007). Ausstehend ist allerdings die Beurteilung, ob Auffälligkeiten auch im MNS zu finden sind. Unter Betrachtung der zugeschriebenen Relevanz des MNS zu sozialen Kognitionsleistungen könnte eine fehlerhafte Funktionsweise eine neurophysiologische Basis für die beeinträchtigte soziale Kognition von schizophrenen Patienten darstellen. Trotz zahlreicher theoretischer Argumente für ein gestörtes MNS bei Patienten mit Schizophrenie (z. B. Arbib & Mundhenk, 2005; Bertrand et al., 2008; Iacoboni & Dapretto, 2006), gibt es nur sehr weni-

ge, einander widersprechende, experimentelle Hinweise, die diese Annahmen bestätigen (siehe Brunet-Gouet et al., 2011). Um jenes Defizit auszugleichen, wurde im Rahmen der vorliegenden Dissertation zusätzlich ein fMRT-Paradigma entwickelt, mit dem gezielt die Integrität des MNS von Patienten im Vergleich zu gesunden Kontrollprobanden untersucht werden konnte (Studie #2, Kapitel 3.).

1.3. Grundlagen der Wahrnehmung eigener Handlungen

Wenn allerdings, wie im vorhergehenden Absatz für das MNS eingehend erläutert, dieselben neuralen Strukturen bei eigenen Handlungen und bei der Wahrnehmung fremder Handlungen aktiviert sind (d. h. „Common Coding“), bestünde die Gefahr, dass fremdinitiierte Aktionen nicht mehr von eigenen unterschieden werden könnten und als Konsequenz die Zuordnung der Handlungen zum richtigen Urheber versagt. Dies wäre vor allem in Situationen problematisch, in denen jemand gleichzeitig eine Handlung ausführt als auch die Selbe bei seinem Gegenüber beobachtet, wie es bei sozialen Interaktionen regelmäßig auftritt (bspw. beim Imitationslernen, Tanzen, Essen). Für solche Fälle muss das Gehirn ein intaktes Kontrollsystem aufweisen, das zuverlässig zwischen „selbst“ und „nicht-selbst“ unterscheidet (Sebanz & Frith, 2004) und damit für das Gefühl der Urheberschaft von Handlungen, Gedanken und Gefühlen verantwortlich ist. Es wird vermutet, dass der von Von Holst und Mittelstaedt (1950) postulierte Efferenzkopiemechanismus (bzw. „Reafferenzprinzip“) diese Aufgabe übernimmt (David et al., 2008; Leube et al., 2012). Der Efferenzkopiemechanismus sagt entsprechend der Theorie die erwarteten sensorischen Konsequenzen eines gegebenen Motorbefehls voraus. Eine Kopie des motorischen Befehls („Efferenzkopie“) wird dazu den sensorischen Arealen übermittelt und dort mit den aktuellen sensorischen Afferenzen („Reafferenz“) verglichen. Wenn beide Signale passen, sind wir Urheber dieser sensorischen Informationen und die Erregbarkeit des betreffenden sensorischen Kortex wird für die sensorische Konsequenz der selbst-produzierten Handlungen abgeschwächt (“Corollary Discharge”, für Reviews siehe Cullen, 2004; Pynn & DeSouza, 2013). Wenn die Signale stattdessen nicht passen, werden die Unterschiede einem anderen Urheber zugeordnet (siehe z. B. Jeannerod & Pacherie, 2004). Die dadurch gewährleistete Eigen-Fremd-Unterscheidung, die scheinbar bei Patienten bei Vorhandensein der Kernsymptomatik der Ich-Störungen nicht zuverlässig gelingt, unterliegt somit der Genauigkeit dieser Vorhersagemodelle.

Mit einer Reihe von Experimenten wurde der Efferenzkopiemechanismus und dessen Beteiligung bei der selbst/nicht-selbst Unterscheidung von Handlungen untersucht (Leube et al., 2010; Synofzik et al., 2010). Darüber hinaus konnte bei Schizophreniepatienten ein klarer Zusammenhang zwischen Ich-Störungen und einer veränderten Funktionsweise dieses Mechanismus gezeigt werden (z. B. Lindner et al., 2005). Man geht davon aus, dass

beim Auftreten entsprechender Symptome die korrekte Vorhersage der sensorischen Konsequenz eigener Handlungen versagt (Synofzik et al., 2010). Beim Abgleich der inakkuraten Vorhersage mit der aktuell wahrgenommenen Konsequenz kommt es zu Diskrepanzen, die fremden Personen zugeschrieben werden und zu Fremdbeeinflussungserleben der Betroffenen führt (z. B. Franck et al., 2001; Frith & Done, 1989; Knoblich et al., 2004; Lindner et al., 2005; Synofzik et al, 2010). Um einen veränderten Abgleichsmechanismus experimentell zu untersuchen, bedarf es non-invasiver, kreativer Annäherungen. Sehr eindrücklich konnte das in einer Studie zum Selbstkitzeln demonstriert werden. Anders als bei gesunden Probanden, wurden von Patienten mit Fremdbeeinflussungserleben selbst produzierte Stimuli nicht als weniger kitzlig empfunden als identische, extern produzierte taktile Stimuli. Der intakte Efferenzkopiemechanismus von Gesunden konnte hingegen die zuständigen sensiblen Hirnareale hemmen und dafür sorgen, dass die Konsequenzen eigener Bewegungen aus der Wahrnehmung herausgerechnet werden (Blakemore et al., 1998; 2000).

Es ist denkbar, dass das MNS und das Efferenzkopiesystem zwei interagierende neuronale Netzwerke sind: Das MNS führt zu einer gemeinsamen Eigen/Fremd-Abbildung, der Efferenzkopiemechanismus zur Eigen/Fremd-Unterscheidung. Die genaue Interaktion der Hirnregionen ist allerdings gegenwärtig noch nicht beschrieben. Strukturell wurde der Abgleichmechanismus, wie auch das MNS, z. B. dem IPL und STS der rechten Hemisphäre zugeordnet (z. B. Farrer et al., 2003; Leube et al., 2003b; 2010). Ziel vorliegender Dissertation war es, in Anlehnung an die Studien von Leube et al. (2003a,b; 2010), dieses Netzwerk weiterführend zu charakterisieren und das neurale Korrelat für einen gestörten Abgleichsmechanismus zu identifizieren. Dabei war von besonderem Interesse, ob das System bei intentionalen Handlungen anders arbeitet als bei Handlungen ohne Ziel und mit welchen Gehirnarealen (z. B. mit dem MNS) es funktionell interagiert (Studie #3, Kapitel 4.).

1.4. Funktionelle Magnetresonanztomografie (fMRT)

Für die Beantwortung offener Fragen wurden drei verschiedene Paradigmen (für eine detaillierte Übersicht siehe weitere Erklärungen in den einzelnen Kapiteln) entworfen und bei einer identischen Stichprobe bestehend aus Patienten mit paranoider Schizophrenie sowie nach Alter, Geschlecht und Bildung parallelisierten Probanden während fMRT-Messungen eingesetzt. Bei dieser indirekten Methode werden über den Sättigungszustand des Hämoglobins im Blut mit Sauerstoff und über damit zusammenhängende magnetische Eigenschaften (BOLD-Kontrast; aus dem Englischen: blood oxygenation level dependent), Rückschlüsse auf aktivierte Hirnareale gezogen. Dabei liegen der Methode folgende Annahmen zugrunde: (1) Erhöhte Neuronenaktivität geht mit der Steigerung des lokalen zerebralen Blutflusses einher, um den Energiebedarf des Gewebes zu kompensie-

ren (Magistretti & Pellerin, 1999), wodurch es zu einem Anstieg an Sauerstoff-gesättigten Blutes kommt, der das messbare BOLD-Signal erhöht. (2) Der Zeitverlauf des Signals folgt einer hämodynamischen Antwortfunktion, die 2 s nach einem neuralen Potential startet und nach 6-9 s ihr Maximum erreicht (Logothetis & Wandell, 2004). (3) Das BOLD Signal korreliert zwar mit Aktionspotentialen, aber deutlicher mit den lokalen Feldpotentialen von Neuronenpopulationen (Logothetis et al., 2001). Daher ist die räumliche und zeitliche Auflösung im Vergleich zu Einzelzellableitungen relativ gering, aber das Verfahren ermöglicht Untersuchungen in größerem räumlichen und zeitlichen Maßstab und damit die Abbildung von Prozessen innerhalb von Netzwerken. Durch geeignete Stimulation durch z. B. visuelle Reize ist es möglich, neurale Korrelate mit einer üblichen Auflösung von 3 mm^3 zu identifizieren, spezielle Netzwerke zu lokalisieren und funktionelle Kopplung von neuralen Systemen zu untersuchen. Neben einfachen Differenzkontrasten zwischen veränderten BOLD-Signalen als Resultat verschiedener Stimulation, wurde in dieser Dissertation auch die funktionelle Konnektivität verschiedener Hirnareale ermittelt. Darunter versteht man die Evaluation temporaler Korrelationen zwischen räumlich getrennten neurophysiologischen Prozessen (Friston, 1994), folglich gemeinsame Signal-Fluktuationen von Hirnarealen, die allerdings keine kausalen Schlussfolgerungen der Wirkungsrichtung erlauben. Zur Bestimmung wurden zwei Ansätze gewählt: Die Seed-Voxel-Analyse (siehe z. B. Bedenbender et al., 2011) und die psychophysiologische Interaktion (PPI, Friston et al., 1997). Letztere erlaubt zusätzlich eine Aussage über Kopplungsveränderungen innerhalb von Netzwerken in Abhängigkeit von der absolvierten Aufgabe.

1.5. Zusammenfassung der Ziele

Da die oben beschriebenen sozial-kognitiven Prozesse von so fundamentaler Bedeutung für eine Teilnahme in der sozialen Gesellschaft sind, ist es außerordentlich wichtig deren neurale Grundlagen zu erforschen und mögliche Defizite bei Patienten mit Schizophrenie zu ergründen, um beispielsweise die Psychopathologie der Erkrankung besser zu verstehen und auf lange Sicht geeignete Therapieansätze zu entwickeln. Auch erlaubt diese Herangehensweise ein besseres Verständnis der Funktionsweise der nicht-pathologischen, zugrundeliegenden Systeme, wenn man Abweichungen in diesen mit der veränderten Pathologie bei Patienten in Zusammenhang bringt. Anders als bei der Mehrheit der Studien zur sozialen Kognition haben wir bei allen drei fMRT-Paradigmen größten Wert auf die Verbesserung der ökologischen Validität der Aufgaben im Rahmen der fMRT-Methode gelegt. So findet man im Alltag beispielsweise selten Situationen vor, in denen Personen nicht-intentionale Handlungen ohne Objekte ausführen oder in denen Intention und Urheberschaft explizit zugeordnet werden müssen, wie es allerdings in den meisten Studien von Teilnehmern erwartet wird. Viele soziale Prozesse laufen aber unterbewusst

und automatisch ab (Nosek et al., 2011). Anders als in anderen Studien, die den Probanden oftmals nur minimale Informationen zur Verfügung stellen, erhielten Teilnehmer in der vorliegenden Studie zur Verarbeitung sozialer Situationen ein realistisches Ausmaß an Informationen (wie z. B. Bewegungsinformationen). Dies ließ sich nur über den Einsatz von Videomaterial gewährleisten.

Zusammenfassend lassen sich die Fragestellungen der Studien wie folgt formulieren: Sind die Netzwerke, die an der Beobachtung von naturalistischer kooperativer Objektmanipulation beteiligt sind, bei Patienten mit Schizophrenie dysfunktional? Kann man die Beteiligung von MNS und ToM System bei der Wahrnehmung von Kooperation zeigen und ist ein bestimmtes Netzwerk bei Patienten dysfunktional (Studie #1)? Ist das mutmaßliche Spiegelneuronensystem, ähnlich wie das ToM-Netzwerk, bei Patienten in seiner Funktionalität beeinflusst? Wenn ja, handelt es sich um regionale Aktivierungsunterschiede oder um eine veränderte Kopplung von Regionen innerhalb dieses Netzwerkes (Studie #2)? Unterscheidet sich während einer impliziten „selbst“ und „nicht-selbst“ Diskriminierung das Aktivitätsmuster im Gehirn von Patienten und gesunden Probanden? Macht es einen Unterschied, ob die beobachteten und ausgeführten Handlungen intentional sind oder kein Ziel haben? Ist dieses Netzwerk in der Kopplung der zugehörigen Areale betroffen und steht es im Zusammenhang mit dem MNS (Studie #3)? Die einzelnen Hypothesen werden in den folgenden drei Kapiteln konkretisiert. Alle diese Fragen sind derzeit ungeklärt und ihre Beantwortung hat neben einem hohen Erkenntnisgewinn für das Feld der sozialen Kognition auch eine große Bedeutung für die Erklärung der verminderten sozialen Funktionsfähigkeit bei Patienten mit Schizophrenie.

Kapitel 2

Studie #1: Wahrnehmung kooperativen Verhaltens

2.1. Hypothesen Studie #1

Um zu untersuchen, welche Netzwerke bei der Wahrnehmung von kooperierendem Verhalten rekrutiert werden, und ob auch dieser Bereich der sozialen Kognition bei schizophrenen Patienten betroffen ist, verwendeten wir ein Paradigma, dass bereits in ähnlicher Form in der Studie von Leube et al. (2012) bei einer gesunden Stichprobe zum Einsatz kam. Patienten mit Schizophrenie und gesunde Kontrollprobanden beobachteten kurze Videoclips mit alltäglichen Handlungen zweier Akteure, die ohne explizite Intentionszuweisung ausschließlich aufmerksam betrachtet werden sollten. Zwei, den Teilnehmern vorher unbekannte, Bedingungen konnten hierbei unterschieden werden: (1) zwei Personen manipulieren kooperativ ein Objekt; (2) eine Person manipuliert das gleiche Objekt während die andere nur beobachtet (siehe Studie #1, Abb. 1). In der Vorgängerstudie von Leube et al. (2012) wurden Gehirnareale identifiziert, die Teil des MNS und für ToM relevante Areale sind, was annehmen lässt, dass für die Wahrnehmung und das Verständnis sozial-kooperativen Verhaltens Spiegelneuronenmechanismen und ToM-Fähigkeiten relevant sind. Wir haben bewusst die Kooperationswahrnehmung gewählt, weil sie eine Untersuchung von MNS und ToM-Netzwerk bei Patienten ermöglicht und es sich um eine sozial-kognitive Komponente handelt, die bei Patienten bisher zu wenig Aufmerksamkeit erfahren hat, obwohl bei ihnen verändertes Kooperationsverhalten bekannt ist (siehe Wischniewski et al., 2009). Wir erhoben zusätzlich die Ausprägung von Verfolgungswahn bei Patienten, um der Frage nachzugehen, ob dieser mit sozialen Wahrnehmungsprozessen im Zusammenhang steht. Folgende Hypothesen (H) wurden im Vorfeld aufgestellt:

H_1: *Bei Probanden sind während der Beobachtung von Kooperation Gehirnareale des MNS aktiv sowie Areale, die zum ToM-Netzwerk gezählt werden.*

H_2: *Patienten mit Schizophrenie rekrutieren bei der Beobachtung der Kooperationsvideos das Netzwerk für die Wahrnehmung kooperativen Verhaltens im Vergleich zu gesunden Probanden vermindert.*

H_3: *Das veränderte Aktivierungsmuster steht zudem im Zusammenhang mit der Ausprägung des Verfolgungswahns bei Patienten mit Schizophrenie.*

2.2. Ergebnisse Studie #1

Wie erwartet konnte gezeigt werden, dass für die Verarbeitung von Kooperation bei gesunden Kontrollprobanden MNS und ToM-Areale verantwortlich sind (H_1). Des Weiteren aktivieren Patienten mit Schizophrenie bekannte ToM-Areale (mPFC, mittlerer cingulärer Kortex, linker angulärer Gyrus (ANG)) bei der Beobachtung von Kooperation im Vergleich zu Kontrollprobanden vermindert (H_2) (siehe Studie #1, Abb. 2-3). Interessanter Weise wurden bei Patienten genau diese Areale bei der Beobachtung der Videos ohne Kooperation verstärkt angesprochen. Sehr wichtig für die Interpretation der Daten ist, dass dieses Hyperaktivierungs-Muster (in pSTS, mPFC, ANG) in der Bedingung ohne Kooperation mit der Ausprägung der Verfolgungswahn-Symptomatik positiv korrelierte (H_3). Ferner konnte diesem Ergebnis entsprechend, ein positiver Zusammenhang zwischen den Selbsteinschätzungen der kognitiven Wahrnehmungsdefizite – ein Maß für subklinische Ausprägung von Wahnsymptomen bei gesunden Kontrollprobanden – und der Aktivierung in diesen Arealen (mPFC, ANG) während der Verarbeitung von Videos ohne Kooperation selbst bei gesunden Probanden gezeigt werden. Das heißt, je stärker die Ausprägung der subklinischen Wahrnehmungsdefizite war, desto stärker wurden bei Beobachtung von non-kooperativen Szenen diese Bereiche aktiviert und waren somit dem Aktivierungsmuster bei Patienten ähnlicher.

2.3. Diskussion Studie #1

Über die Bestätigung der Ergebnisse von Leube et al. (2012) bei gesunden Probanden (sprich: der Co-Aktivierung von ToM und MNS-Arealen) hinaus, konnten wir mit Studie #1 zeigen, dass Patienten bei der Wahrnehmung von Kooperation vor allem innerhalb des ToM-Netzwerkes Defizite aufweisen, nicht aber im MNS. Das wichtigste Ergebnis ist allerdings die Hyperaktivierung innerhalb des ToM-Netzwerkes als Folge der Beobachtung nicht-kooperierender Akteure – der ursprünglichen Kontrollbedingung. Die aktivierten Regionen bei Patienten sind solche, die bei Gesunden bereits mit Kooperationsaufgaben in Zusammenhang gebracht wurden (z. B. Brüne et al., 2011; Decety et al., 2004; Elliot et al., 2006; Lissek et al., 2008). Die Korrelation des Aktivierungsmusters mit der Ausprägung des Verfolgungswahns belegt experimentell die Theorie der Hyperintentionalität oder “Hyper-ToM” von Abu-Akel und Bailey (2000). Diese besagt, dass Patienten mit Schizophrenie mentale Zustände überattribuieren und exzessive Hypothesen über Intentionen anderer bilden. Im Bezug auf unsere Studie scheint es zu einer Hyperaktivität des Mentalisierungs-Netzwerkes gekommen zu sein während die Akteure im Video nicht kooperierten. Der Zusammenhang mit Verfolgungswahn deutet darauf hin, dass diese mehrdeutige Situation von Patienten in einer paranoiden Art verarbeitet wurde, d. h. Misstrauen erweckt hat

und dadurch intensiv nach sozialen Hinweisen gesucht wurde, um verstärkt mögliche Intentionen der Akteure zu verarbeiten – und das individuell umso stärker, je ausgeprägter der Verfolgungswahn der Patienten war. Dass ähnliches Videomaterial, mit zwei unabhängig agierenden Akteuren, implizit paranoide Reaktionen bei Schizophreniepatienten auslösen kann, ist darüber hinaus bekannt (Park et al., 2011).

Ein paar Studien, die Hyperintentionalität bei Patienten als möglichen Erklärungsansatz für gestörte Mentalisierungs-Fähigkeiten heranziehen, existieren bereits (Blakemore et al., 2003; Montag et al., 2011; Russell et al., 2006; Walter et al., 2009). Allerdings fanden nur wenige bisher einen direkten Zusammenhang zwischen Mentalizing-Defiziten und der Wahnsymptomatik (Blackwood et al., 2001; Harrington et al., 2005a; Park et al., 2011). Unsere Ergebnisse unterstützen die Theorie von Wible (2012) und Wible et al. (2009) nach der insbesondere eine Hyperaktivität des pSTS und des IPL (beinhaltet ANG) zur fehlerhaften Wahrnehmung von Intentionen und gesteigerter Zuordnung von Signifikanz zu Handlungen anderer führen könnten – und damit Wahnsymptome am besten erklären. Andere Autoren fanden ebenfalls Hyperaktivierungen im pSTS in ihrer sozial-kognitiven Kontrollbedingung und diskutierten diese im Zusammenhang mit Wahnsymptomen (Mier et al., 2008; Pinkham et al., 2008; Walter et al., 2009). Wir konnten den Zusammenhang zwischen Verfolgungswahn und hyperaktivem ToM-Netzwerk vor allem für den pSTS, mPFC und ANG erstmals belegen.

Interessanter Weise scheint ähnliches auch für Individuen zuzutreffen, die subklinische Wahrnehmungsbeeinträchtigungen haben – auch als schizotype Persönlichkeitsmerkmale bezeichnet. Diese treten in der allgemeinen Bevölkerung auf (Claridge, 1997; Stefanis et al., 2002) und spiegeln ein biologisches Maß für die Psychose-Anfälligkeit wieder (Vollema et al., 2002). In Ergänzung zu Studien, die eine verändere ToM-Netzwerk Aktivierung für Individuen mit verstärkter Psychose-Anfälligkeit zeigen (z. B. Modinos et al., 2010), konnten wir, ähnlich wie für Schizophreniepatienten, einen Zusammenhang zwischen subklinischen Wahrnehmungsstörungen und verstärkter ToM-Aktivierung bei Kontrollprobanden aufzeigen. Daher trägt dieses Ergebnis maßgeblich zur Diskussion bei, ob ein beeinträchtigtes Mentalisierungs-Netzwerk das Risiko für Schizophrenie erhöht (siehe Bora et al., 2009; Brüne, 2005; Penn et al., 2008) und im Speziellen für die Entstehung von Verfolgungswahn verantwortlich ist.

Kapitel 3

Studie #2: Funktionsfähigkeit des Spiegelneuronensystems

3.1. Hypothesen Studie #2

Soziale Defizite von schizophrenen Patienten werden in der Literatur häufig mit einer gestörten Funktionsweise des MNS erklärt (z. B. Kato & Mimura, 2012). Das vorherige Kapitel und die Befundlage in der bestehenden Literatur (z. B. Bora et al., 2009) suggerieren jedoch, dass während sozialer Informationsverarbeitung vordergründig das ToM-Netzwerk beeinträchtigt ist und somit eher die Intentionen von Handlungen nicht richtig interpretiert werden können. Vom MNS wird angenommen, dass es sich um ein Netzwerk handelt, das im Gegensatz zum ToM-Netzwerk für basalere Handlungswahrnehmung zuständig ist (Brass et al., 2007; Kilner & Frith, 2008; Liepelt et al., 2008; Van Overwalle & Baetens, 2009). Es verarbeitet die Ausführung eigener Bewegungen sowie die Beobachtung entsprechender Bewegungen bei anderen Akteuren (siehe Kapitel 1.2.). Um die Funktionsweise dieses Systems bei Patienten fokussiert zu untersuchen, wurde ein fMRT-Paradigma entwickelt: Während der BOLD-Kontrast gemessen wurde, sollten die Versuchspersonen Videos eines Schauspielers, der eine Schachfigur greift und jeweils auf ein bestimmtes Feld eines „Mini-Schachbretts“ setzt, beobachten. Abwechselnd mit dieser Bedingung sollten sie selber nach der Schachfigur greifen und auf ein Feld setzen, entweder wie vorher beobachtet oder auf ein anderes, durch ein bestimmtes Monitorsymbol indiziertes Feld (siehe Studie #2, Abb. 1). Durch eine Analyse der Gehirnregionen, die entsprechend der „Common Coding“ Theorie in beiden Bedingungen (Beobachten und Ausführen) aktiviert sind, kann man das MNS kartieren und Aktivierungsunterschiede zwischen Patienten und Probanden ermitteln. Da derzeitige Hinweise in der Literatur für lokale Aktivierungsunterschiede sehr rar sind (Brunet-Gouet et al., 2011) und zusätzlich aus – mit fMRI schwer zu vergleichenden – elektrophysiologischen Studien stammen (Enticott et al., 2008b; McCormick et al., 2012; Schürmann et al., 2007), sollte neben klassischen Aktivierungsunterschieden zusätzlich das

MNS (Ausgangsregionen: bilateraler IFG & IPL) mittels funktioneller Konnektivitätsanalysen auf dessen Funktionalität untersucht werden (für methodisches Vorgehen siehe Studie #2, Kapitel 2.4.). Folgende Hypothesen wurden geprüft:

H_4: *Beobachten und Ausführen einer zielgerichteten Handlung führt bei Patienten und Probanden zur Aktivierung von MNS-assoziierten Arealen (z. B. pSTS, IFG, IPL), bei Patienten geschieht dies in geringerem Ausmaß.*

H_5: *Eher als spezifische lokale Aktivierungsunterschiede, liegt innerhalb des MNS eine Dyskonnektivität der beteiligten Regionen vor.*

3.2. Ergebnisse Studie #2

Beobachten und Ausführen einer zielgerichteten Greifbewegung führte bei Patienten und Probanden wie erwartet zur Aktivierung typischer MNS-assoziierter Areale, v. a. pSTS, IFG, IPL und präzentraler Gyrus (vgl. Metaanalyse von Molenberghs et al., 2012). Bei Patienten war die Ausdehnung des rekrutierten Netzwerkes allerdings erwartungsgemäß geringer (H_4). Ein signifikanter Aktivierungsunterschied konnte für ein rechts-hemisphärisches Cluster im Lingualen Gyrus (LNG), mit Ausweitung in den posterioren Parahippocampalen Gyrus, gezeigt werden. Dieses Cluster erfüllte bei Probanden zumindest Eigenschaften von MNS-Arealen: Es war stark aktiviert bei Beobachtung sowie bei Ausführung einer Greifbewegung. Bei Patienten wurde dieses Cluster allerdings deutlich schwächer während eigener Greifbewegungen angesprochen (siehe Studie #2, Abb. 2). Des Weiteren konnten wir im Vergleich zu Probanden innerhalb des MNS hypothesenkonform signifikant verringerte funktionelle Konnektivität der Ausgangsregionen bilateraler IPL (1) und rechter IFG (2) zu anderen Regionen innerhalb des MNS bei Patienten zeigen: (1) zu rechtslateralen Regionen IFG und pSTS und (2) zum rechten pSTS und linken Präzentralem Gyrus (siehe Studie #2, Tab. 2 & Abb. 3) (H_6). Zusätzlich war auch die Konnektivität zwischen LNG und rechtem IFG und bilateralem IPL bei Patienten signifikant verringert.

3.3. Diskussion Studie #2

Der differenziell aktivierte Linguale Gyrus ist kein typisches Spiegelneuronen-Areal, obwohl er in unserer und anderen Studien Spiegeleigenschaften aufweist (z. B. Pfeifer et al., 2008; Van der Gaag et al., 2007; Wild et al., 2003; Williams et al., 2006) sowie häufig in Studien berichtet wird, in denen Imitation Untersuchungsgegenstand ist (Lee et al., 2006; Koski et al., 2003). Wir wissen nicht, ob der LNG tatsächlich Spiegelneurone beinhaltet, jedoch der benachbarte Parahippocampus – in den sich das differenziell aktivierte Cluster ausdehnt – wie in Ableitungsstudien am menschlichen Kortex eindrücklich gezeigt wurde (Mukamel

et al., 2010). Allerdings spiegeln unsere Daten nicht zwangsläufig ein spezifisches MNS-Defizit wider. Da der LNG Teil des ventralen Pfades für visuelle Informationsverarbeitung ist (Mishkin et al., 1983) und in das Encodieren visueller Informationen für einen späteren Gedächtnisabruf sowie in mentale Rotationen involviert ist (Schendan & Stern, 2008), deutet das Ergebnis auf Netzwerkdefizite in der frühen sensorischen Verarbeitung bei Patienten mit Schizophrenie hin. Interessanter Weise ist diese Region bei Gesunden funktionell mit Regionen des klassischen MNS verbunden, während bei Patienten eine verminderte Konnektivität zwischen LNG und MNS-Regionen vorliegt. Eine funktionale Kopplung von visuellen und motorischen Arealen wurde in einer aktuellen Studie beschrieben (Pavlidou et al., 2012), wobei Assoziationsareale im parietalen Lobus den visuellen Kortex beeinflussen, indem z. B. propriozeptive Informationen zurück projiziert werden (Astafiev et al., 2004; Macaluso et al., 2000), um die visuelle Verarbeitung zu aktualisieren (Schippers & Keysers, 2011). Ein Informationsaustausch in die andere Richtung – vom LNG zum IPL – könnte dazu dienen, die gegenwärtige Wahrnehmung einer Handlung mit der internen Repräsentation dieser Handlungen im MNS abzugleichen (Schendan & Stern, 2008). Bei Patienten mit Schizophrenie legt die Dyskonnektivität zwischen IPL und LNG nahe, dass entsprechende Wege des Informationsaustausches gestört sind. Wir konnten darüber hinaus zeigen, dass die Kommunikation zwischen bekannten MNS-Arealen, die normalerweise multidirektional Informationen austauschen (Schippers & Keysers, 2011), beeinträchtigt zu sein scheint. Auch der in Kapitel 1.3. beschriebene Efferenzkopiemechanismus ist auf einen Informationsaustausch zwischen den betroffenen Regionen angewiesen, v. a. über die Inputregion des MNS (pSTS), die eine Efferenzkopie vom fronto-parietalen MNS erhält (Iacoboni et al., 2001; Iacoboni & Dapretto, 2006; Leube et al., 2003a; Molenberghs et al., 2010). Daher könnte es sein, dass die verminderte Konnektivität auch Zeichen eines gestörten Efferenzkopiemechanismus ist. Dieser Sachverhalt wurde in Studie #3 aufgegriffen.

Kapitel 4

Studie #3: Wahrnehmung verzögerter Eigenhandlungen

4.1. Hypothesen Studie #3

Eine Annäherung an den mutmaßlich defizitären Efferenzkopiemechanismus, der „Fremd“ und „Eigen“ unterscheiden kann (siehe Kapitel 1.3), stellt die Untersuchung eines Mechanismus dar, der Unstimmigkeiten (d. h. einen experimentell eingeführten Mismatch) zwischen motorischer Ausführung und tatsächlich wahrgenommenem visuellen Feedback detektiert (Nahab et al., 2011). Um diesen zu untersuchen, führten wir abwechselnd zu zeitgetreuem Feedback eine zeitliche Diskrepanz (200 ms) zwischen aktuell ausgeführter kontinuierlicher Handbewegung und visuellem Feedback der Bewegung über ein Monitorsystem ein (siehe Studie #3, Abb. 1). Eine ähnliche Manipulation kam bereits bei Leube et al. (2003a; 2010) zum Einsatz. In deren Studie waren bewegungssensitive Hirnregionen bei Gesunden dann stärker aktiv, wenn das beobachtete Feedback zur aktuellen Handlung um 200 Millisekunden zeitversetzt präsentiert wurde, als wenn Feedback und Handlung synchron waren. Es kam durch die eigene Bewegung zu einer Abschwächung der Aktivierung in Bewegungsarealen bei gesunden Probanden (Leube et al. 2003a, 2010), nicht aber bei Patienten. Patienten registrierten eher eine zeitliche Verschiebung des Feedbacks, wenn es gar nicht modifiziert war. Sie akzeptierten zeitversetztes Feedback eher als synchrones Resultat als es gesunde Probanden taten. Offen blieb, welche neuralen Defizite bei Patienten dieser toleranteren zeitlicher Bindung zwischen Feedback und Ausführung zugrunde liegen. Um darüber hinaus zu untersuchen, ob sich die Verarbeitung von intenti-

onalen und unintentionalen Handlungen unterschieden (wie es für das MNS beschrieben wurde, z. B. Iacoboni et al., 2005), wurden neben des nicht-intentionalen Faustschlusses zielgerichtete Greifbewegungen mit einer Schachfigur untersucht, die jeweils kontinuierlich mit einer Frequenz von 1 Hz durchgeführt wurden. Die Untersuchung der funktionellen Konnektivität der beteiligten Areale und von intentionalen Greifbewegungen könnte einen Aufschluss über die Interaktion von MNS und Efferenzkopiemechanismus liefern. Folgende Hypothesen sollten hauptsächlich untersucht werden.

H_6: *Besteht ein Mismatch zwischen ausgeführter Bewegung und eigenem Feedback, kommt es bei intentionalen Bewegungen bei gesunden Probanden zu einer verstärkten Aktivierung bewegungssensitiver Areale, nicht aber bei Patienten mit Schizophrenie.*

H_7: *Da das MNS vor allem für intentionale Handlungen sensitiv ist, erwarten wir bei der Ausführung und Beobachtung zielgerichteter Greifbewegung von Gesunden eine Beteiligung des MNS. Bei der Verarbeitung zeitlicher Diskrepanzen sollte eine Kontrollinstanz identifiziert werden können, die die „selbst/nicht-selbst"-Unterscheidung in diesem System gewährleistet – das üblicherweise eigene und fremde Handlungen in denselben neuralen Strukturen gleichermaßen abbildet.*

H_8: *Die funktionelle Konnektivität zwischen Arealen, die eine Efferenzkopie senden und bewegungssensitiven Zielregionen, deren Reaktionen laut Theorie durch die Efferenzkopie für synchrones Feedback selbstproduzierter Handlungen abgeschwächt werden, ist bei Patienten verringert.*

H_9: *Veränderungen innerhalb des Efferenzkopie-Netzwerks stehen im Zusammenhang mit der Ausprägung der Ich-Störungs-Symptomatik bei Patienten.*

4.2. Ergebnisse Studie #3

Für Patienten im Vergleich zu Kontrollprobanden fanden wir in der Interaktionsanalyse Gruppe x Bedingung ein signifikant verändertes Aktivierungsmuster im rechten IFG pars Opercularis. Dabei handelt es sich um eine Region, die sowohl dem Mismatch-Mechanismus als auch dem MNS zugeordnet wird (Mismatch: Leube et al., 2003b; 2010; Schnell et al., 2007; Yomogida et al., 2010; MNS: z. B. Kilner et al., 2009). Die Signaländerung des IFG zu den einzelnen Bedingungen (mit/ohne Verzögerung; intentional/nicht-intentional) zeigte, dass diese bewegungssensitive Region mit motorischen Funktionen (Binkofski & Buccino, 2004) bei Gesunden stärker aktiviert ist, wenn eine zeitliche Diskrepanz zwischen ausgeführter intentionaler Bewegung und visuellem Feedback vorliegt, während der IFG in der Reaktion auf zeitgetreues Feedback abgeschwächt war (H_7). Für nicht-intentionale Faustschluss-Bewegungen ergab sich keine solche Modulation. Der IFG von Patienten wies ein gegensätzliches Aktivierungsmuster auf – verstärkte Aktivierung bei zeitgetreu-

em Feedback und geringere Aktivierung als Antwort auf zeitverzögertes Feedback (siehe Studie #3, Abb. 2) (H_6).

Wir untersuchten den IFG auf funktionelle Konnektivität mit dem gesamten Gehirn und mit einer „Region of Interest" Analyse und verwendeten bedingungsabhängige (psychophysiologische Interaktionsanalyse, PPI) und bedingungsunabhängige (Seed-voxel) Methoden. Für die bedingungsabhängige Analyse konnte gezeigt werden, dass bei Patienten der IFG bei verzögertem Feedback weniger mit dem ventromedialen Präfrontalen Kortex funktionell verbunden ist als es bei Probanden der Fall ist (H_8). Zudem korrelierte die veränderte Aktivierung in dieser Zielregion mit der individuellen Ausprägung der Ich-Störungen (H_9). Die bedingungsunabhängige Analyse ergab geringere funktionelle Konnektivität mit den links-hemisphärischen Strukturen Insula und Putamen bei Patienten (H_8; siehe Studie #3, Abb. 3).

4.3. Diskussion Studie #3

Auch in einer Vorgängerstudie von Leube et al. (2003b) wurde dem IFG eine Rolle bei der Detektion einer Diskrepanz zwischen eigener Handlung und visuellem Feedback zugeschrieben, sowie in anderen Studien für die Detektion von visuell-motorischer Inkongruenz (Schnell et al., 2007), sensorischem Mismatch (Yomogida et al., 2010) und für den Sinn der Urheberschaft (David et al., 2008). Am ehesten entsprechen unseren Ergebnisse aber denen von Macuga und Frey (2011), die zeigten, dass der IFG anders auf eigenes visuelles „live" Feedback repetitiver Handbewegungen reagierte als auf nahezu identisches Videomaterial, in welchem dieselbe Bewegung von einem anderen Akteur ausgeführt wurde. Mit unseren Ergebnissen können wir die Argumentation dieser Autoren unterstützen: Sie nehmen an, dass der IFG auf Grundlage von subtilen räumlich-zeitlichen Unterschieden zwischen vorhergesagtem und aktuellem sensorischen Feedback zwischen fremd und eigen unterscheidet. Darüber hinaus konnten wir zeigen, dass das vor allem auf intentionale Bewegungen zutrifft. Mit seiner Antwortcharakteristik ist der IFG ein potentieller Teil des Efferenzkopie-Mechanismus: Er ist gehemmt während eigenem nicht-verzögerten Feedback, vermutlich aufgrund der Kongruenz zwischen vorhergesagter Konsequenz und aktuell wahrgenommener Konsequenz. Zusätzlich ist er bei zeitlich inkongruentem Feedback, das potentiell nicht zur eigenen Vorhersage der Konsequenzen dieser Greifbewegungen passt, stark aktiviert. Denkbar ist, dass der IFG für diesen Abgleich vorher eine Efferenzkopie von höheren motorischen Arealen, z. B. dem Putamen bekommt (Leube et al., 2003a; 2010). Als Teil des MNS könnte der IFG den Mechanismus beherbergen, mit dessen Hilfe aufgrund von zeitlichen Eigenschaften des Feedbacks zwischen Fremd und Eigen unterschieden werden kann – obwohl üblicherweise fremd und eigen gleichermaßen im MNS abgebildet werden (z. B. Kilner et al., 2009).

Der IFG bei Patienten mit Schizophrenie wies sowohl ein anderes Aktivitäts- als auch ein verändertes Konnektivitätsmuster mit anderen Bereichen im Gehirn auf. Dass bei Patienten die Empfindungen von selbst-generierten Bewegungen nicht ordnungsgemäß abgeschwächt werden, wurde schon in anderen Studien gezeigt (z. B. Blakemore et al., 2000; Shergill et al., 2005). Eine mögliche Erklärung dafür lässt sich aus unseren Daten ableiten. Es ist denkbar, dass „Corollary Discharge"-Signale den IFG nicht rechtzeitig erreichen, um die sensorisch-evozierte Aktivität abzuschwächen. Dies könnte auch erklären, warum der IFG bei nicht-verzögertem Feedback bei Patienten stärker rekrutiert wird. Wenn man annimmt, dass die Verzögerung im Bereich von 200 ms liegt, könnte das auch erklären, warum der IFG weniger stark auf verzögertes Feedback anspricht und somit auch einen Erklärungsansatz dafür liefern, dass Patienten eine Verzögerung im Feedback wahrnehmen, obwohl keine vorliegt (siehe Leube et al., 2010). Die Argumentation wird unterstützt davon, dass bereits zeitliche Verzögerungen der Weiterleitung des „Corollary Discharge"-Signals zu sensorischen Kortizes bei Patienten in der Größenordnung von 50 ms aufgezeigt werden konnten (Whitford et al., 2011; 2012). Dieser Effekt wurde von den Autoren durch strukturelle Konnektivitätsdefizite im Frontallappen erklärt. Wir konnten jene Annahme mit unseren funktionellen Analysen bestätigen. Der Orbitofrontale Kortex (OFC) war während der Bedingung mit zeitlicher Verzögerung weniger stark mit dem IFG verbunden. Dieser Region wurde bereits früher eine Rolle bei der expliziten Zuordnung von Urheberschaft (Miele et al., 2011; Moll et al., 2007), insbesondere aber bei eigenen Handlungen (van der Meer et al., 2010) zugeschrieben. Da der OFC direktes somatisches und visuelles Feedback erhält (Kringelbach & Rolls, 2004), ist es denkbar, dass diese benötigten Informationen für den Abgleichmechanismus durch die verminderte Konnektivität zum IFG nicht rechtzeitig bereit stehen. Dass die entsprechende Veränderung im Zusammenhang mit dem Fremdbeeinflussungserleben steht, demonstriert die Korrelation der Aktivität des OFC mit der Ausprägung der Ich-Störungs-Symptomatik.

Darüber hinaus fanden wir weitere Dyskonnektivitäten zum Putamen, der für die Bildung von Vorhersagen über das zeitliche Eintreffen des Feedbacks zuständig ist (Leube et al., 2003a; 2010) und zur Insula, die interozeptives Feedback verarbeitet und bereitstellt (Wylie & Tregellas, 2010; van der Meer et al., 2010). Zusätzlich deuten unsere Ergebnisse auf ein generelles Problem beim Austausch von relevanten Feedback-Signalen und Vorhersagen über Konsequenzen ausgeführter Handlungen hin, die zur Unterscheidung des Feedbacks von „selbst" versus „nicht-selbst" im IFG benötigt werden.

Kapitel 5

Generelle Diskussion

5.1. Zusammenfassende Diskussion

Zusammenfassend konnten wir zur Klärung vieler offener Fragen bezüglich der Wahrnehmung von eigenen und fremden Handlungen und deren Beeinträchtigung bei Patienten mit Schizophrenie beitragen. Bei der Kooperationswahrnehmung war von den beteiligten MNS und ToM-Netzwerk vor allem letzteres bei Patienten in seiner Funktionalität eingeschränkt. Es zeigte sich, dass anders als bei Gesunden dieses Netzwerk gerade im nicht-kooperativen Kontext verstärkt – und bei der Beobachtung von Kooperation hingegen weniger – aktiviert war. Ersteres stand mit der Verfolgungswahnsymptomatik im Zusammenhang und bekräftigte die Annahme, dass Patienten mit paranoider Schizophrenie übermentalisieren bzw. Hyper-ToM aufweisen (Abu-Akel, 1999; Frith, 2004). Eine Tendenz dazu fanden wir bereits bei Gesunden, die subklinische Wahrnehmungsdefizite aufwiesen, was darauf hinweist, dass das ToM-Netzwerk eine wichtige Rolle bei der Ausprägung von Verfolgungswahn einnimmt.

Mit einem spezielleren Fokus auf die Funktionalität des MNS konnten wir mit einem anderen Paradigma auch erstmals mit einer fMRT-Studie MNS-Defizite aufzeigen. Wie er-

wartet, spiegelten sich diese nicht primär in regionalen Aktivierungsunterschieden wieder, sondern in einer generell verminderten Kopplung zwischen den beteiligten MNS-Arealen, insbesondere zwischen IFG, IPL, pSTS sowie einer okzipitalen Region mit Spiegeleigenschaften, dem Lingualen Gyrus. Dieses Ergebnis deutet auf einen gestörten Austausch von sensorischer Information hin, der für eine korrekte interne Repräsentation von Handlungen essentiell ist. Da das MNS als Grundlage für sozial-kognitive Fähigkeiten weitestgehend akzeptiert ist (Gallese & Sinigaglia, 2011; Iacoboni & Dapretto, 2006), könnte die hier demonstrierte, v. a. rechts-lateralisierte Dyskonnektivität, den sozial-kognitiven Beeinträchtigungen bei Patienten maßgeblich zugrunde liegen – d. h. beispielsweise deren Imitations- (z. B. Park et al., 2008), Mentalisierungs- (z. B. Das et al., 2012) und Empathiefähigkeiten (e.g., Varcin et al., 2010) negativ beeinflussen. Laut Fett et al. (2011), führt eine Verminderung dieser Fähigkeiten zu einer verringerten sozialen Funktionsfähigkeit bei Patienten.

Des Weiteren konnte eine Region identifiziert werden, die es gesunden Individuen ermöglicht, innerhalb des MNS auf Basis zeitlicher Eigenschaften des Feedbacks zwischen „selbst“ und „nicht-selbst“ zu unterscheiden: der rechte IFG. Dieses Ergebnis bezog sich ausschließlich auf intentionale Greifbewegungen mit einem Objekt, für die, wie man weiß, auch das MNS vor allem sensitiv ist (Iacoboni et al., 2005). Bei Patienten war der Mechanismus allerdings in umgekehrter Weise verändert bzw. verzögert: Es zeigte sich fehlende Hemmung des IFG, wenn Feedback und ausgeführte Handlung zeitlich übereinstimmten, und verringerten Aktivierung, wenn sie zeitlich inkongruent auftraten. Begleitet wurde dieses Ergebnis von einer Verminderung der funktionellen Konnektivität mit Arealen, die normaler Weise Abschwächungssignale („Corollary Discharges“) sowie externe und interne Feedback-Signale für einen Abgleichmechanismus bereitstellen. Wir nehmen aufgrund unserer Daten an, dass der IFG und die hier demonstrierte Dyskonnektivität neurale Korrelate für das Versagen des Efferenzkopiemechanismus bei Patienten mit Schizophrenie darstellen. Die gestörte Verarbeitung der sensorischen Diskrepanz kann zu Selbst-Monitoring-Defiziten und Fehlzuweisungen der Urheberschaft beitragen und daraus resultierenden Beeinflussungswahn bei Patienten erklären. Dass es einen solchen Zusammenhang – zwischen verändertem Netzwerk und der Psychopathologie – gibt, konnte ebenfalls gezeigt werden.

5.2. Limitationen

Die vorgestellten Studien weisen einige kritische Punkte auf, die bei der Interpretation der Daten berücksichtigt werden sollten. Als erstes wäre zu nennen, dass das MNS ein Konstrukt ist, das ursprünglich von Forschungsergebnissen beim Affen abgeleitet wurde. Tatsächlich ist aber die Befundlage für ein Vorhandensein des MNS im Menschen sehr überzeugend (Kilner et al., 2009; Rizzolatti & Sinigaglia, 2010). Allerdings ist die Rolle, die

für das MNS postuliert wird, nicht unumstritten (Hickok, 2009). Besonders schwer sind die Interpretationen, wenn man das MNS mittels Bildgebungsverfahren (mit begrenzter räumlicher Auflösung) untersucht (z. B. Turella et al., 2009), da diese Verfahren nur die summierte Aktivierung einer Vielzahl von Neuronen innerhalb eines Voxels darstellen können. Für einen Voxel, der während Beobachtung sowie Ausführung aktivert ist, könnte das im Extremfall bedeuten, dass die eine Hälfte der Neuronen des Voxels für eigene Handlungen rekrutiert wird, während die andere für die Repräsentation fremder Handlungen zuständig ist. Jene „zwei Populationen"-Hypothese ist allerdings höchst unwahrscheinlich, da man davon ausgehen müsste, dass anders als bei Affen in motorischen Arealen eine Vielzahl von sensorischen Neurone eingestreut sein müssten und diese nicht mit den motorischen Neuronen kommunizieren würden (Rizzolatti & Fabbri-Destro, 2010).

Dass die Ergebnisse unserer fMRT-Studie mit denen von einer Vielzahl an MNS-Studien übereinstimmen, die Zellableitungen (Mukamel et al., 2010) und Elektroenzephalographie (z. B. Oberman et al., 2007) verwendeten, spricht dafür fMRT-Untersuchungen als zu solchen Maßnahmen ergänzende Methode zur Studie von MNS-Prozessen zu nutzen (Bartels et al., 2008). Ferner besteht eine erstaunliche Übereinstimmung zwischen auf fMRT-Daten angewandte Konnektivitätsanalysen, bei denen gemeinsame Signalfluktuationen in räumlich getrennten Regionen statistisch untersucht werden, und Studien zur strukturellen Konnektivität (Greicius et al., 2009).

Grundsätzlich hat die gewählte Methodik weitere Schwachstellen. Unter anderem handelt es sich um ein sehr indirektes Messverfahren (vgl. Punkt 1.4.) und die Zusammenhänge zwischen zerebralem Blutfluss, BOLD und neuronaler Aktivität sind noch immer nicht eindeutig geklärt (Ekstrom, 2010). Neben der bereits angesprochenen geringen räumlichen Auflösung besteht das Problem der zeitlichen Auflösung, da das Abtasten des BOLD-Signals üblicherweise auf nur ca. alle 2 s methodisch limitiert ist, während die Interaktionen zwischen Neuronen nur auf die Frequenz derer Aktionspotentiale begrenzt ist. Somit filtert diese Methode sehr kurz andauernde Signale heraus und neurale Vorgänge werden eher auf einem makroskopischen Level untersucht.

Eine weitere Einschränkung ist, dass wir neben klinischen Interviews und einer ToM-Aufgabe kein weiteres Maß zur sozialen Funktionsfähigkeit der Patienten und Probanden erhoben haben und uns deshalb vor allem auf die Literatur beziehen müssen. Diese zeigt allerdings eindrücklich, dass Patienten in den sozialen Kognitionsdomänen – Kooperation (z. B. Wischniewski et al., 2009), Imitation (z. B. Park et al., 2008) und Eigen/Fremdunterscheidung (z. B. Jeannerod, 2009) – Defizite aufweisen. Nicht unproblematisch ist darüber hinaus, dass alle Patienten medikamentös behandelt wurden. Allerdings wurde in allen drei Studien der Einfluss von Medikamenten auf das individuelle Aktivierungsmuster mittels Korrelationsanalyse untersucht. Es wurde kein Zusammenhang gefunden. Darüber

hinaus scheinen Antipsychotika keinen generellen Einfluss auf den BOLD-Kontrast zu haben (Röder et al., 2010). Für eine bessere Generalisierbarkeit sollten unsere Befunde allerdings zusätzlich an unmedizierten Patienten repliziert werden.

5.3. Bedeutung

Der wichtigste Befund aus den hier vorgestellten Studien ist der Zusammenhang zwischen erhöhter Aktivierung im ToM-Netzwerk während der Kontrollbedingung (pSTS, ANG, mPFC) und Verfolgungswahn bei Patienten (Studie #1). Er bekräftigt nun auch experimentell die oft bemühte Theorie der Entstehung von Verfolgungswahn aufgrund von Übermentalisierung (Abu-Akel, 1999; Frith, 2004). Diese Erkenntnis ermöglicht somit ein besseres Verständnis für die Entstehung der paranoiden Symptomatik von schizophrenen Patienten.

Das Ergebnis eines gestörten MNS (Studie #2) wird maßgeblich die Forschung im Bereich der sozialen Kognition bei Patienten mit Schizophrenie beeinflussen, da nun ein experimenteller fMRT-Hinweis für die veränderte Integrität des MNS vorliegt. An diesem Punkt sollte zukünftig angeknüpft und der Einfluss einer veränderten Funktionsweise des MNS auf die soziale Funktionsfähigkeit quantifiziert werden. Das Ergebnis stellt des Weiteren eine Möglichkeit dar, die Erfolge von Therapien, die soziale Fähigkeiten verbessern sollen (bspw. Kurtz & Richardson, 2012), auch neuronal begleitet zu messen. Der Befund ist auch bedeutend für die Klassifikation der Schizophrenie: Die Störung des MNS stellt eine weitere Domäne dar, in denen sich Patienten mit Autismus-Spektrum-Störungen (ASS) und Schizophrenie in der beeinträchtigten sozialen Kognition phänomenologisch ähneln. Weitere Gemeinsamkeiten sind beispielsweise genetische Veränderungen (Guilmatre et al., 2009) und ToM-Defizite (Couture et al., 2010), die zusammen mit dem geteilten MNS-Defizit (siehe für ASS z. B. Perkins et al., 2010) zu der Annahme von gemeinsamen ätiologischen Wurzeln beitragen (siehe Review in King & Lord, 2011).

Die wichtigste Erkenntnis der letzten Studie (Studie #3) stellt das Ergebnis dar, dass der IFG aufgrund seiner Charakteristik einen Kontrollmechanismus innerhalb des MNS beherbergen könnte, nach dem bereits länger gesucht wird (David et al., 2008; Leube et al., 2012). Dieser Kontrollmechanismus ist bei Patienten, vermutlich aufgrund der hier gezeigten, veränderten Konnektivität mit entsprechenden Inputregionen, dysfunktional. Dadurch könnten beispielsweise die Phänomene des Beeinflussungserlebens innerhalb der Ich-Störungssymptomatik erklärt werden.

5.4. Ausblick

Aus unseren Ergebnissen lassen sich neue weitergehende Forschungsfragen ableiten.

Zu der Ich-Symptomatik gehören beispielsweise auch die Symptome Gedankeneingabe und Gedankenentzug, bei denen Patienten die Urheberschaft von Gedanken nicht klar zuordnen können (Jeannerod, 2009). Ob eine fehlerhafte Zuweisung von Gedanken ebenfalls einem Defizit des Efferenzkopiemechanismus zugeordnet werden kann, wurde bisher lediglich theoretisch angenommen, aber noch nicht empirisch untersucht (Frith, 2012). Zwar konnte gezeigt werden, dass die Ausprägung der Ich-Störungen, die Gedankenentzug und –eingabe umfassen, mit einer Beeinträchtigung des Efferenzkopiemechanismus bei motorischen Handlungen einhergehen (z. B. Lindner et al., 2005), allerdings kann daraus ein Zusammenhang für die zugrunde liegenden Mechanismen der Zuordnung von Gedanken nur indirekt abgeleitet werden. Die Entwicklung eines neuen Paradigmas, bei dem anstatt einer motorischen Aufgabe Gedanken untersucht werden, ist für den direkten Nachweis notwendig – stellt allerdings auch eine sehr herausfordernde Aufgabe dar.

Interessant wäre darüber hinaus, ob die Zuordnung von mentalen Zuständen zu sich selbst und anderen, d. h. ToM-Mechanismen, ebenfalls einem solchen Mechanismus unterliegen (vgl. Williams & Happé, 2009). Um phänomenologische Ähnlichkeiten bzw. Unterschiede zu ASS, mit Hyposozialität, oder Williams Syndrom, mit Hypersozialität (Jawaid et al., 2012), weiter zu untersuchen, wäre es wichtig diese Patientengruppen für einen Vergleich in zukünftige Studien einzuschließen. Des Weiteren haben wir uns in Studie #1 auf die Wahrnehmung von kooperativen Verhalten fokussiert. Da im sozialen Kontext nicht nur Kooperation beobachtet, sondern tatsächlich auch daran teilgenommen wird, wäre es notwendig eine fMRT-Studie zu entwickeln, bei der ein interaktives Paradigma eingesetzt wird. Die Teilnehmer sollten hierbei tatsächlich mit anderen Teilnehmern kooperieren müssen, wie es beispielsweise durch gemeinsames Computerspielen bei gesunden Probanden realisiert wurde (siehe hierzu Emonds et al., 2012). Hierbei wäre anzunehmen, dass bei Patienten ebenfalls das ToM-Netzwerk betroffen ist. Primär sollte in zukünftigen Studien ein noch stärkerer Fokus auf die Zusammenarbeit und Trennung der überlappenden Funktionen der drei Systeme (Mentalisierung, Efferenzkopiemechanismus, „Common Coding“) während sozialer-Kognition gelegt werden.

Kapitel 6

Referenzen

Abu-Akel, A., & Bailey, A. L. (2000). The possibility of different forms of theory of mind impairment in psychiatric and developmental disorders. *Psychological medicine*, *30*, 735–8.

Abu-Akel, A. (1999). Impaired theory of mind in schizophrenia. *Pragmatics & Cognition*, *7*, 247–282.

Adolphs, R. (2001). The neurobiology of social cognition. *Current Opinion in Neurobiology*, *11*, 231–239.

Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature reviews. Neuroscience*, *7*, 268–77.

Apperly, I. A. (2008). Beyond Simulation-Theory and Theory-Theory: why social cognitive neuroscience should use its own concepts to Study "theory of mind". *Cognition*, *107*, 266–83.

Arbib, M. A., & Mundhenk, T. N. (2005). Schizophrenia and the mirror system: an essay. *Neuropsychologia*, *43*, 268–80.

Astafiev, S. V., Stanley, C. M., Shulman, G. L., & Corbetta, M. (2004). Extrastriate body area in human occipital cortex responds to the performance of motor actions. *Nature neuroscience*, *7*, 542–8.

Bartels, A., Logothetis, N. K., & Moutoussis, K. (2008). fMRI and its interpretations: an illustration on directional selectivity in area V5/MT. *Trends in neurosciences*, *31*, 444–53.

Bedenbender, J., Paulus, F. M., Krach, S., Pyka, M., Sommer, J., Krug, A., … Jansen, A. (2011). Functional connectivity analyses in imaging genetics: considerations on methods and data interpretation. (Y. He, Ed.) *PloS one*, *6*, e26354.

Bentall, R. P., & Kaney, S. (1989). Content specific information processing and persecutory delusions: an investigation using the emotional Stroop test. *The British journal of medical psychology*, *62 (Pt 4)*, 355–64.

Bertrand, M.-C., Achim, A. M., Harvey, P.-O., Sutton, H., Malla, A. K., & Lepage, M. (2008). Structural neural correlates of impairments in social cognition in first episode psychosis. *Social neuroscience*, *3*, 79–88.

Bertrand, M.-C., Sutton, H., Achim, A. M., Malla, A. K., & Lepage, M. (2007). Social cognitive impairments in first episode psychosis. *Schizophrenia research*, *95*, 124–33.

Binkofski, F., Amunts, K., Stephan, K. M., Posse, S., Schormann, T., Freund, H.-J., … Seitz, R. J. (2000). Broca's region subserves imagery of motion: A combined cytoarchitectonic and fMRI Study. *Human Brain Mapping*, *11*, 273–285.

Binkofski, F., & Buccino, G. (2004). Motor functions of the Broca's region. *Brain and language*, *89*, 362–9.

Blackwood, N. J., Howard, R. J., Bentall, R. P., & Murray, R. M. (2001). Cognitive neuropsychiatric models of persecutory delusions. *The American journal of psychiatry*, *158*, 527–39.

Blakemore, S. J., Smith, J., Steel, R., Johnstone, C. E., & Frith, C. D. (2000). The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. *Psychological medicine*, *30*, 1131–9.

Blakemore, S. J., Wolpert, D. M., & Frith, C. D. (1998). Central cancellation of self-produced tickle sensation. *Nature neuroscience*, *1*, 635–40.

Blakemore, S. J., Boyer, P., Pachot-Clouard, M., Meltzoff, A., Segebarth, C., & Decety, J. (2003). The detection of contingency and animacy from simple animations in the human brain. *Cerebral cortex (New York, N.Y. : 1991)*, *13*, 837–44.

Bora, E., Yucel, M., & Pantelis, C. (2009). Theory of mind impairment in schizophrenia: meta-analysis. *Schizophrenia research*, *109*, 1–9.

Brakoulias, V., & Starcevic, V. (2008). A cross-sectional survey of the frequency and characteristics of delusions in acute psychiatric wards. *Australasian psychiatry : bulletin of Royal Australian and New Zealand College of Psychiatrists*, *16*, 87–91.

Brunet, E., Sarfati, Y., Hardy-Baylé, M. C., & Decety, J. (2000). A PET investigation of the attribution of intentions with a nonverbal task. *NeuroImage*, *11*, 157–66.

Brunet-Gouet, E., Achim, A. M., Vistoli, D., Passerieux, C., Hardy-Baylé, M.-C., & Jackson, P. L. (2011). The Study of social cognition with neuroimaging methods as a means to explore future directions of deficit evaluation in schizophrenia? *Psychiatry research*, *190*, 23–31.

Brüne, M. (2005). "Theory of mind" in schizophrenia: a review of the literature. *Schizophrenia bulletin*, *31*, 21–42.

Brüne, M., Ozgürdal, S., Ansorge, N., Von Reventlow, H. G., Peters, S., Nicolas, V., … Lissek, S. (2011). An fMRI Study of “theory of mind” in at-risk states of psychosis: comparison with manifest schizophrenia and healthy controls. *NeuroImage*, *55*, 329–37.

Buccino, G., Binkofski, F., Fink, G. R., Fadiga, L., Fogassi, L., Gallese, V., … Freund, H.-J. (2001). Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI Study. *European Journal of Neuroscience*, *13*, 400–404.

Castelli, F., Happé, F., Frith, U., & Frith, C. (2000). Movement and mind: a functional imaging Study of perception and interpretation of complex intentional movement patterns. *NeuroImage*, *12*, 314–25.

Cattaneo, L., Barchiesi, G., Tabarelli, D., Arfeller, C., Sato, M., & Glenberg, A. M. (2011). One’s motor performance predictably modulates the understanding of others’ actions through adaptation of premotor visuo-motor neurons. *Social cognitive and affective neuroscience*, *6*, 301–10.

Ciaramidaro, A., Adenzato, M., Enrici, I., Erk, S., Pia, L., Bara, B. G., & Walter, H. (2007). The intentional network: how the brain reads varieties of intentions. *Neuropsychologia*, *45*, 3105–13.

Claridge, G. (1997). *Schizotypy: Implications for illness and health.* (G. Claridge, Ed.) (p. xii 340 pp.). Oxford: Oxford University Press.

Corcoran, R., Mercer, G., & Frith, C. D. (1995). Schizophrenia, symptomatology and social inference: investigating “theory of mind” in people with schizophrenia. *Schizophrenia research*, *17*, 5–13.

Couture, S. M., Penn, D. L., Losh, M., Adolphs, R., Hurley, R., & Piven, J. (2010). Comparison of social cognitive functioning in schizophrenia and high functioning autism: more convergence than divergence. *Psychological medicine*, *40*, 569–79.

Cullen, K. E. (2004). Sensory signals during active versus passive movement. *Current opinion in neurobiology*, *14*, 698–706.

Das, P., Lagopoulos, J., Coulston, C. M., Henderson, A. F., & Malhi, G. S. (2012). Mentalizing impairment in schizophrenia: a functional MRI Study. *Schizophrenia research*, *134*, 158–64.

David, N., Newen, A., & Vogeley, K. (2008). The “sense of agency” and its underlying cognitive and neural mechanisms. *Consciousness and cognition*, *17*, 523–34.

De Lange, F. P., Spronk, M., Willems, R. M., Toni, I., & Bekkering, H. (2008). Complementary systems for understanding action intentions. *Current biology : CB*, *18*, 454–7.

Decety, J., Jackson, P. L., Sommerville, J. A., Chaminade, T., & Meltzoff, A. N. (2004). The neural bases of cooperation and competition: an fMRI investigation. *NeuroImage*, *23*, 744–51.

Dinstein, I., Hasson, U., Rubin, N., & Heeger, D. J. (2007). Brain areas selective for both observed and executed movements. *Journal of neurophysiology*, *98*, 1415–27.

Ekstrom, A. (2010). How and when the fMRI BOLD signal relates to underlying neural activity: the danger in dissociation. *Brain research reviews*, *62*, 233–44.

Elliott, R., Völlm, B., Drury, A., McKie, S., Richardson, P., & Deakin, J. F. W. (2006). Co-operation with another player in a financially rewarded guessing game activates regions implicated in theory of mind. *Social neuroscience*, *1*, 385–95.

Emonds, G., Declerck, C. H., Boone, C., Vandervliet, E. J. M., & Parizel, P. M. (2012). The cognitive demands on cooperation in social dilemmas: an fMRI Study. *Social neuroscience*, *7*, 494–509.

Enticott, P. G., Hoy, K. E., Herring, S. E., Johnston, P. J., Daskalakis, Z. J., & Fitzgerald, P. B. (2008). Reduced

motor facilitation during action observation in schizophrenia: a mirror neuron deficit? *Schizophrenia research*, *102*, 116–21.

Enticott, P. G., Johnston, P. J., Herring, S. E., Hoy, K. E., & Fitzgerald, P. B. (2008). Mirror neuron activation is associated with facial emotion processing. *Neuropsychologia*, *46*, 2851–4.

Farrer, C., Franck, N., Georgieff, N., Frith, C. D., Decety, J., & Jeannerod, M. (2003). Modulating the experience of agency: a positron emission tomography Study. *NeuroImage*, *18*, 324–333.

Farrer, C., & Franck, N. (2007). Self-Monitoring in Schizophrenia. *Current Psychiatry Reviews*, *3*, 9.

Fear, C., Sharp, H., & Healy, D. (1996). Cognitive processes in delusional disorders. *The British journal of psychiatry : the journal of mental science*, *168*, 61–7.

Fett, A.-K. J., Viechtbauer, W., Dominguez, M.-G., Penn, D. L., Van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neuroscience and biobehavioral reviews*, *35*, 573–88.

Ford, J. M., & Mathalon, D. H. (2004). Electrophysiological evidence of corollary discharge dysfunction in schizophrenia during talking and thinking. *Journal of psychiatric research*, *38*, 37–46.

Franck, N., Farrer, C., Georgieff, N., Marie-Cardine, M., Daléry, J., D'Amato, T., & Jeannerod, M. (2001). Defective Recognition of One's Own Actions in Patients With Schizophrenia. *American Journal of Psychiatry*, *158*, 454–459.

Freeman, D. (2007). Suspicious minds: the psychology of persecutory delusions. *Clinical psychology review*, *27*, 425–57.

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage*, *6*, 218–29.

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*, *2*, 56–78.

Frith, C. D., & Frith, U. (1999). Interacting minds--a biological basis. *Science*, *286*, 1692–5.

Frith, C. D. (2004). Schizophrenia and theory of mind. *Psychological Medicine*, *34*, 385–389.

Frith, C. D. (2012). Explaining delusions of control: the comparator model 20 years on. *Consciousness and cognition*, *21*, 52–4.

Frith, C. D. (1992). *The cognitive neuropsychology of schizophrenia.* (N. Hillsdale, Ed.) (p. xiv 169 pp.). UK: Psychology Press.

Frith, C. D., & Corcoran, R. (2009). Exploring "theory of mind" in people with schizophrenia. *Psychological Medicine*, *26*, 521.

Frith, C. D., & Done, D. J. (2009). Experiences of alien control in schizophrenia reflect a disorder in the central monitoring of action. *Psychological Medicine*, *19*, 359.

Frith, U., & Frith, C. D. (2003). Development and neurophysiology of mentalizing. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *358*, 459–73.

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain*, *119*, 593–609.

Gallese, V., & Sinigaglia, C. (2011). What is so special about embodied simulation? *Trends in cognitive sciences*, *15*, 512–9.

Green, M. F., & Horan, W. P. (2010). Social Cognition in Schizophrenia. *Current Directions in Psychological Science*, *19*, 243–248.

Green, M. F., Bearden, C. E., Cannon, T. D., Fiske, A. P., Hellemann, G. S., Horan, W. P., … Nuechterlein, K. H. (2012). Social cognition in schizophrenia, Part 1: performance across phase of illness. *Schizophrenia bulletin*, *38*, 854–64.

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral cortex (New York, N.Y. : 1991)*, *19*, 72–8.

Guilmatre, A., Dubourg, C., Mosca, A.-L., Legallic, S., Goldenberg, A., Drouin-Garraud, V., … Campion, D. (2009). Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrenia, autism, and mental retardation. *Archives of general psychiatry*, *66*, 947–56.

Harrington, L., Langdon, R., Siegert, R. J., & McClure, J. (2005a). Schizophrenia, theory of mind, and persecutory delusions. *Cognitive neuropsychiatry*, *10*, 87–104.

Harrington, L., Siegert, R. J., & McClure, J. (2005b). Theory of mind in schizophrenia: a critical review. *Cognitive neuropsychiatry*, *10*, 249–86.

Hesse, M. D., Sparing, R., & Fink, G. R. (2009). End or means--the “what” and “how” of observed intentional actions. *Journal of cognitive neuroscience*, *21*, 776–90.

Hickok, G. (2009). Eight Problems for the Mirror Neuron Theory of Action Understanding in Monkeys and Humans. Retrieved from http://www.mitpressjournals.org/doi/full/10.1162/jocn.2009.21189

Iacoboni, M., Koski, L. M., Brass, M., Bekkering, H., Woods, R. P., Dubeau, M. C., … Rizzolatti, G. (2001). Reafferent copies of imitated actions in the right superior temporal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *98*, 13995–9.

Iacoboni, M. (1999). Cortical Mechanisms of Human Imitation. *Science*, *286*, 2526–2528.

Iacoboni, M., & Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. *Nature reviews. Neuroscience*, *7*, 942–51.

Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J. C., & Rizzolatti, G. (2005). Grasping the intentions of others with one’s own mirror neuron system. *PLoS biology*, *3*, e79.

Jawaid, A., Riby, D. M., Owens, J., White, S. W., Tarar, T., & Schulz, P. E. (2012). “Too withdrawn” or “too friendly”: considering social vulnerability in two neuro-developmental disorders. *Journal of Intellectual Disability Research*, *56*, 335–350.

Jeannerod, M. (2009). The sense of agency and its disturbances in schizophrenia: a reappraisal. *Experimental brain research. Experimentelle Hirnforschung. Expérimentation cérébrale*, *192*, 527–32.

Jeannerod, M., & Pacherie, E. (2004). Agency, Simulation and Self-identification. *Mind and Language*, *19*, 113–146.

Kato, Y., & Mimura, M. (2012). Disturbance of social interaction in patients with psychosis—A review of the role of malfunction of the mirror neuron system. *Journal of Oral Biosciences*, *54*, 14–11.

Kato, Y., Muramatsu, T., Kato, M., Shibukawa, Y., Shintani, M., & Mimura, M. (2011). Magnetoencephalography Study of right parietal lobe dysfunction of the evoked mirror neuron system in antipsychotic-free schizophrenia. *PloS one*, *6*, e28087.

Keysers, C., & Gazzola, V. (2007). Integrating simulation and theory of mind: from self to social cognition. *Trends in cognitive sciences*, *11*, 194–6.

Kilner, J. M., Friston, K. J., & Frith, C. D. (2007). Predictive coding: an account of the mirror neuron system. *Cognitive processing*, *8*, 159–66.

Kilner, J. M., Neal, A., Weiskopf, N., Friston, K. J., & Frith, C. D. (2009). Evidence of mirror neurons in human inferior frontal gyrus. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *29*, 10153–9.

King, B. H., & Lord, C. (2011). Is schizophrenia on the autism spectrum? *Brain research*, *1380*, 34–41.

Knoblich, G., Stottmeister, F., & Kircher, T. (2004). Self-monitoring in patients with schizophrenia. *Psychological medicine*, *34*, 1561–9.

Koski, L., Iacoboni, M., Dubeau, M.-C., Woods, R. P., & Mazziotta, J. C. (2003). Modulation of cortical activity during different imitative behaviors. *Journal of neurophysiology*, *89*, 460–71.

Kringelbach, M. L., & Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in neurobiology*, *72*, 341–72.

Kurtz, M. M., & Richardson, C. L. (2012). Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. *Schizophrenia bulletin*, *38*, 1092–104.

Lee, T.-W., Josephs, O., Dolan, R. J., & Critchley, H. D. (2006). Imitating expressions: emotion-specific neural substrates in facial mimicry. *Social cognitive and affective neuroscience*, *1*, 122–35.

Leube, D. T., Knoblich, G., Erb, M., Grodd, W., Bartels, M., & Kircher, T. T. J. (2003). The neural correlates of perceiving one's own movements. *NeuroImage*, *20*, 2084–2090.

Leube, D. T., Straube, B., Green, A., Blümel, I., Prinz, S., Schlotterbeck, P., & Kircher, T. T. J. (2012). A possible brain network for representation of cooperative behavior and its implications for the psychopathology of schizophrenia. *Neuropsychobiology*, *66*, 24–32.

Leube, Dirk T, Knoblich, G., Erb, M., & Kircher, T. T. J. (2003). Observing one's hand become anarchic: an fMRI Study of action identification. *Consciousness and cognition*, *12*, 597–608.

Leube, D. T., Knoblich, G., Erb, M., Schlotterbeck, P., & Kircher, T. T. J. (2010). The neural basis of disturbed efference copy mechanism in patients with schizophrenia. *Cognitive Neuroscience*, *1*, 111–117.

Li, H., Chan, R. C. K., McAlonan, G. M., & Gong, Q. (2010). Facial emotion processing in schizophrenia: a meta-analysis of functional neuroimaging data. *Schizophrenia bulletin*, *36*, 1029–39.

Liew, S.-L., Han, S., & Aziz-Zadeh, L. (2011). Familiarity modulates mirror neuron and mentalizing regions during intention understanding. *Human brain mapping*, *32*, 1986–97.

Lindenmayer, J.-P., McGurk, S. R., Khan, A., Kaushik, S., Thanju, A., Hoffman, L., … Herrmann, E. (2013). Improving social cognition in schizophrenia: a pilot intervention combining computerized social cognition training with cognitive remediation. *Schizophrenia bulletin*, *39*, 507–17.

Lindner, A., Thier, P., Kircher, T. T. J., Haarmeier, T., & Leube, D. T. (2005). Disorders of agency in schizophrenia correlate with an inability to compensate for the sensory consequences of actions. *Current biology : CB*, *15*, 1119–24.

Lissek, S., Peters, S., Fuchs, N., Witthaus, H., Nicolas, V., Tegenthoff, M., … Brüne, M. (2008). Cooperation and deception recruit different subsets of the theory-of-mind network. *PloS one*, *3*, e2023.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*, 150–7.

Logothetis, N. K., & Wandell, B. A. (2004). Interpreting the BOLD signal. *Annual review of physiology*, *66*, 735–69.

Läge, D., Egli, S., Riedel, M., & Möller, H.-J. (2012). Exploring the structure of psychopathological symptoms: a re-analysis of AMDP data by robust nonmetric multidimensional scaling. *European archives of psychiatry and clinical neuroscience*, *262*, 227–38.

Macaluso, E., Frith, C. D., & Driver, J. (2000). Modulation of Human Visual Cortex by Crossmodal Spatial Attention. *Science*, *289*, 1206–1208.

Macuga, K. L., & Frey, S. H. (2011). Selective responses in right inferior frontal and supramarginal gyri differentiate between observed movements of oneself vs. another. *Neuropsychologia*, *49*, 1202–7.

Maeda, T., Kato, M., Muramatsu, T., Iwashita, S., Mimura, M., & Kashima, H. (2012). Aberrant sense of agency in patients with schizophrenia: forward and backward over-attribution of temporal causality during intentional action. *Psychiatry research*, *198*, 1–6.

Magistretti, P. J., & Pellerin, L. (1999). Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *354*, 1155–63.

McCormick, L. M., Brumm, M. C., Beadle, J. N., Paradiso, S., Yamada, T., & Andreasen, N. (2012). Mirror neuron function, psychosis, and empathy in schizophrenia. *Psychiatry research*, *201*, 233–9.

Miele, D. B., Wager, T. D., Mitchell, J. P., & Metcalfe, J. (2011). Dissociating neural correlates of action monitoring and metacognition of agency. *Journal of cognitive neuroscience*, *23*, 3620–36.

Mier, D., Sauer, C., Lis, S., Esslinger, C., Wilhelm, J., Gallhofer, B., & Kirsch, P. (2008). Neuronal correlates of affective theory of mind in schizophrenia out-patients: evidence for a baseline deficit. *Psychological Medicine*, *40*, 1607–1617.

Mishkin, M., Ungerleider, L. G., & Macko, K. A. (1983). Object vision and spatial vision: two cortical pathways. *Trends in Neurosciences*, *6*, 414–417.

Modinos, G., Renken, R., Shamay-Tsoory, S. G., Ormel, J., & Aleman, A. (2010). Neurobiological correlates of theory of mind in psychosis proneness. *Neuropsychologia*, *48*, 3715–24.

Molenberghs, P., Brander, C., Mattingley, J. B., & Cunnington, R. (2010). The role of the superior temporal sulcus and the mirror neuron system in imitation. *Human brain mapping*, *31*, 1316–26.

Molenberghs, P., Cunnington, R., & Mattingley, J. B. (2012). Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neuroscience and biobehavioral reviews*, *36*, 341–9.

Moll, J., De Oliveira-Souza, R., Garrido, G. J., Bramati, I. E., Caparelli-Daquer, E. M. A., Paiva, M. L. M. F., … Grafman, J. (2007). The self as a moral agent: linking the neural bases of social agency and moral sensitivity. *Social neuroscience*, *2*, 336–52.

Montag, C., Dziobek, I., Richter, I. S., Neuhaus, K., Lehmann, A., Sylla, R., … Gallinat, J. (2011). Different aspects of theory of mind in paranoid schizophrenia: evidence from a video-based assessment. *Psychiatry research*, *186*, 203–9.

Moutoussis, M., Williams, J., Dayan, P., & Bentall, R. P. (2007). Persecutory delusions and the conditioned avoidance paradigm: towards an integration of the psychology and biology of paranoia. *Cognitive neuropsychiatry*, *12*, 495–510.

Mukamel, R., Ekstrom, A. D., Kaplan, J., Iacoboni, M., & Fried, I. (2010). Single-neuron responses in humans during execution and observation of actions. *Current biology : CB*, *20*, 750–6.

Muñoz, M., Sanz, M., Pérez-Santos, E., & Quiroga, M. de L. Á. (2011). Proposal of a socio-cognitive-behavioral structural equation model of internalized stigma in people with severe and persistent mental illness. *Psychiatry research*, *186*, 402–8.

Nahab, F. B., Kundu, P., Gallea, C., Kakareka, J., Pursley, R., Pohida, T., … Hallett, M. (2011). The neural processes underlying self-agency. *Cerebral cortex (New York, N.Y. : 1991)*, *21*, 48–55.

Nosek, B. A., Hawkins, C. B., & Frazier, R. S. (2011). Implicit social cognition: from measures to mechanisms. *Trends in cognitive sciences*, *15*, 152–9.

Oberman, L. M., Pineda, J. A., & Ramachandran, V. S. (2007). The human mirror neuron system: a link between action observation and social skills. *Social cognitive and affective neuroscience*, *2*, 62–6.

Ostrom, T. M. (1984). The sovereignty of social cognition. Handbook of social cognition (pp. 1–38).

Otte, E., Jost, K., Habel, U., & Koch, I. (2011). Exploring cross-task compatibility in perceiving and producing facial expressions using electromyography. *Acta psychologica*, *138*, 187–92.

Park, I. H., Ku, J., Lee, H., Kim, S. Y., Kim, S. I., Yoon, K. J., & Kim, J.-J. (2011). Disrupted theory of mind network processing in response to idea of reference evocation in schizophrenia. *Acta psychiatrica Scandinavica*, *123*, 43–54.

Park, S., Matthews, N., & Gibson, C. (2008). Imitation, simulation, and schizophrenia. *Schizophrenia bulletin*, *34*, 698–707.

Pavlidou, A., Schnitzler, A., & Lange, J. (2012). Interactions between visual and motor areas during the recognition of plausible actions as revealed by magnetoencephalography. *Human brain mapping*. doi:10.1002/hbm.22207

Penn, D. L., Sanna, L. J., & Roberts, D. L. (2008). Social cognition in schizophrenia: an overview. *Schizophrenia bulletin*, *34*, 408–11.

Perkins, T., Stokes, M., McGillivray, J., & Bittar, R. (2010). Mirror neuron dysfunction in autism spectrum disorders. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*, *17*, 1239–43.

Pfeifer, J. H., Iacoboni, M., Mazziotta, J. C., & Dapretto, M. (2008). Mirroring others' emotions relates to empathy and interpersonal competence in children. *NeuroImage*, *39*, 2076–85.

Pinkham, A. E., Hopfinger, J. B., Pelphrey, K. A., Piven, J., & Penn, D. L. (2008). Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. *Schizophrenia research*, *99*, 164–75.

Platek, S. M., Keenan, J. P., Gallup, G. G., & Mohamed, F. B. (2004). Where am I? The neurological correlates of self and other. *Brain research. Cognitive brain research*, *19*, 114–22.

Pynn, L. K., & Desouza, J. F. X. (2013). The function of efference copy signals: implications for symptoms of schizophrenia. *Vision research*, *76*, 124–33.

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. *Annual review of neuroscience*, *27*, 169–92.

Rizzolatti, G., & Fabbri-Destro, M. (2010). Mirror neurons: from discovery to autism. *Experimental brain research. Experimentelle Hirnforschung. Expérimentation cérébrale*, *200*, 223–37.

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Cognitive Brain Research*, *3*, 131–141.

Rizzolatti, G., & Sinigaglia, C. (2010). The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. *Nature reviews. Neuroscience*, *11*, 264–74.

Russell, T. A., Reynaud, E., Herba, C., Morris, R., & Corcoran, R. (2006). Do you see what I see? Interpretations of intentional movement in schizophrenia. *Schizophrenia research*, *81*, 101–11.

Röder, C. H., Hoogendam, J. M., & Van der Veen, F. M. (2010). FMRI, antipsychotics and schizophrenia. Influence of different antipsychotics on BOLD-signal. *Current pharmaceutical design*, *16*, 2012–25.

Saha, S., Chant, D., & McGrath, J. (2008). Meta-analyses of the incidence and prevalence of schizophrenia: conceptual and methodological issues. *International journal of methods in psychiatric research*, *17*, 55–61.

Saxe, R. (2006). Uniquely human social cognition. *Current opinion in neurobiology*, *16*, 235–9.

Schendan, H. E., & Stern, C. E. (2008). Where vision meets memory: prefrontal-posterior networks for visual object constancy during categorization and recognition. *Cerebral cortex (New York, N.Y. : 1991)*, *18*, 1695–711.

Schimansky, J., Rössler, W., & Haker, H. (2012). The influence of social cognition on ego disturbances in patients with schizophrenia. *Psychopathology*, *45*, 117–25.

Schippers, M. B., Gazzola, V., Goebel, R., & Keysers, C. (2009). Playing charades in the fMRI: are mirror and/or mentalizing areas involved in gestural communication? (G. Chapouthier, Ed.)*PloS one*, *4*, e6801.

Schippers, M. B., & Keysers, C. (2011). Mapping the flow of information within the putative mirror neuron system during gesture observation. *NeuroImage*, *57*, 37–44.

Schulte-Rüther, M., Markowitsch, H. J., Fink, G. R., & Piefke, M. (2007). Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. *Journal of cognitive neuroscience*, *19*, 1354–72.

Schürmann, M., Järveläinen, J., Avikainen, S., Cannon, T. D., Lönnqvist, J., Huttunen, M., & Hari, R. (2007). Manifest disease and motor cortex reactivity in twins discordant for schizophrenia. *The British journal of psychiatry : the journal of mental science*, *191*, 178–9.

Sebanz, N., & Frith, C. (2004). Beyond simulation? Neural mechanisms for predicting the actions of others. *Nature neuroscience*, *7*, 5–6.

Shergill, S. S., Samson, G., Bays, P. M., Frith, C. D., & Wolpert, D. M. (2005). Evidence for sensory prediction deficits in schizophrenia. *The American journal of psychiatry*, *162*, 2384–6.

Sprong, M., Schothorst, P., Vos, E., Hox, J., & Van Engeland, H. (2007). Theory of mind in schizophrenia: meta-analysis. *The British journal of psychiatry : the journal of mental science*, *191*, 5–13.

Spunt, R. P., & Lieberman, M. D. (2012). Dissociating modality-specific and supramodal neural systems for action understanding. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *32*, 3575–83.

Startup, M., & Startup, S. (2005). On two kinds of delusion of reference. *Psychiatry research*, *137*, 87–92.

Stefanis, N. C., Hanssen, M., Smirnis, N. K., Avramopoulos, D. A., Evdokimidis, I. K., Stefanis, C. N., … Van Os, J. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological medicine*, *32*, 347–58.

Synofzik, M., Thier, P., Leube, D. T., Schlotterbeck, P., & Lindner, A. (2010). Misattributions of agency in schizophrenia are based on imprecise predictions about the sensory consequences of one's actions. *Brain : a journal of neurology*, *133*, 262–71.

Turella, L., Pierno, A. C., Tubaldi, F., & Castiello, U. (2009). Mirror neurons in humans: consisting or confounding evidence? *Brain and language*, *108*, 10–21.

Van der Gaag, C., Minderaa, R. B., & Keysers, C. (2007). Facial expressions: what the mirror neuron system can and cannot tell us. *Social neuroscience*, *2*, 179–222.

Van der Meer, L., Costafreda, S., Aleman, A., & David, A. S. (2010). Self-reflection and the brain: a theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. *Neuroscience and biobehavioral reviews*, *34*, 935–46.

Van Overwalle, F., & Baetens, K. (2009). Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. *NeuroImage*, *48*, 564–84.

Varcin, K. J., Bailey, P. E., & Henry, J. D. (2010). Empathic deficits in schizophrenia: The potential role of rapid facial mimicry. *Journal of the International Neuropsychological Society*, *16*, 621–629.

Vollema, M. G., Sitskoorn, M. M., Appels, M. C. M., & Kahn, R. S. (2002). Does the Schizotypal Personality Questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophrenia research*, *54*, 39–45.

Von Holst, E., & Mittelstaedt, H. (1950). Das Reafferenzprinzip. *Die Naturwissenschaften*, *37*, 464–476.

Walter, H., Ciaramidaro, A., Adenzato, M., Vasic, N., Ardito, R. B., Erk, S., & Bara, B. G. (2009). Dysfunction of the social brain in schizophrenia is modulated by intention type: an fMRI Study. *Social cognitive and affective neuroscience*, *4*, 166–76.

Whitford, T. J., Mathalon, D. H., Shenton, M. E., Roach, B. J., Bammer, R., Adcock, R. A., … Ford, J. M. (2011). Electrophysiological and diffusion tensor imaging evidence of delayed corollary discharges in patients with schizophrenia. *Psychological medicine*, *41*, 959–69.

Whitford, T. J., Ford, J. M., Mathalon, D. H., Kubicki, M., & Shenton, M. E. (2012). Schizophrenia, myelination, and delayed corollary discharges: a hypothesis. *Schizophrenia bulletin*, *38*, 486–94.

Wible, C. G., Preus, A. P., & Hashimoto, R. (2009). A Cognitive Neuroscience View of Schizophrenic Symptoms: Abnormal Activation of a System for Social Perception and Communication. *Brain imaging and behavior*, *3*, 85–110.

Wible, C. G. (2012). Schizophrenia as a disorder of social communication. *Schizophrenia research and treatment*, *2012*, 920485.

Wild, B., Erb, M., Eyb, M., Bartels, M., & Grodd, W. (2003). Why are smiles contagious? An fMRI Study of the interaction between perception of facial affect and facial movements. *Psychiatry Research: Neuroimaging*, *123*, 17–36.

Williams, D. M., & Happé, F. (2009). What Did I Say? Versus What Did I Think? Attributing False Beliefs to Self Amongst Children With and Without Autism. *Journal of Autism and Developmental Disorders*, *39*, 865–873.

Williams, J. H. G., Waiter, G. D., Gilchrist, A., Perrett, D. I., Murray, A. D., & Whiten, A. (2006). Neural mechanisms of imitation and "mirror neuron" functioning in autistic spectrum disorder. *Neuropsychologia*, *44*, 610–21.

Wischniewski, J., Windmann, S., Juckel, G., & Brüne, M. (2009). Rules of social exchange: game theory, individual differences and psychopathology. *Neuroscience and biobehavioral reviews*, *33*, 305–13.

Wylie, K. P., & Tregellas, J. R. (2010). The role of the insula in schizophrenia. *Schizophrenia research*, *123*, 93–104.

Yomogida, Y., Sugiura, M., Sassa, Y., Wakusawa, K., Sekiguchi, A., Fukushima, A., … Kawashima, R. (2010). The neural basis of agency: an fMRI Study. *NeuroImage*, *50*, 198–207.

Angenommene Artikel

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Kapitel 7

Manuskripte #1-3

Hyperintentionality during automatic perception of naturalistic cooperative behavior in patients with schizophrenia*

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Manuskript #1

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Abstract

Social cognition and the corresponding functionality of involved brain networks are essential for effortless social interaction. Patients with schizophrenia exhibit impaired social functioning. In this study, we focused on the neural networks involved in the automatic perception of cooperative behavior and their alterations in schizophrenia.

We performed a functional magnetic resonance imaging study of 19 schizophrenia patients and 19 healthy matched controls. Participants watched a set of short videos with two actors manipulating objects, either with (C+) or without cooperation (C-). Additionally, we assessed delusional symptoms in patients using the Scales for the Assessment of Positive Symptoms and psychosis proneness in healthy controls using the brief Schizotypal Personality Questionnaire.

The observed group-by-condition interaction revealed a contrasting activation pattern for patients versus healthy controls in the medial and lateral prefrontal cortex, the middle cingulate cortex and the left angular gyrus. Furthermore, increased activation of the middle prefrontal areas, left angular gyrus, and the posterior sulcus temporalis superior in response to the non-cooperative condition (C-) was positively correlated with delusional symptoms in patients.

Our findings suggest an overactivated Theory of Mind network in patients for the processing of non-cooperative behavior. Thus, "overmentalizing" might be based on delusions and altered processing of cooperative behavior in patients with schizophrenia.

Keywords: Cooperative Behavior | Persecutory Delusion | fMRI | Schizophrenia | ToM

Introduction

Social cognition is a key function of human beings. Successfully taking part in social interactions is of great importance for survival. Hence, we have a need for constant screening of social contexts and meanings. Therefore, our brain should be well adapted to these processes. A number of important brain regions linked to social perception have been identified. Among others, areas related to a core aspect of social cognition, namely "theory of mind" (ToM, originally proposed by Premack & Woodruff, 1978; Baron-Cohen, 1995), are of great importance. ToM refers to the ability to predict and explain other people's behavior on the basis of an understanding of their intention. Central ToM regions are the temporo-parietal junction (TPJ) and precuneus/posterior cingulate cortex (Ciaramidaro et al., 2007; U. Frith & C.D. Frith, 2003; Saxe, 2006). However, most specific for mentalizing is the medial prefrontal cortex (BA 8/9 mPFC) and its subregion the paracingulate cortex (BA 32, Amodio & Frith, 2006; C.D. Frith & U. Frith, 2006). Additionally, a crucial element of social cognition is action understanding, which is proposed to recruit the mirror neuron system (MNS; Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Rizzolatti, Fogassi, & Gallese, 2001). This network consists of neurons that discharge during action production as well as during observation of a similar action performed by another actor (in monkeys: Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996; in humans: Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010). One particular function of these neurons is their responsiveness to observations of goal-directed interactions of a hand with an object (Gallese et al., 1996; Iacoboni et al., 2005). Associated brain areas for this action execution/observation matching system are the inferior frontal gyrus (BA 44) and rostral parts of the inferior parietal lobe, areas beneath the intraparietal sulcus (aIPS), and their input region the posterior part of the superior temporal sulcus (pSTS) (for reviews see Fabbri-Destro & Rizzolatti, 2008; Iacoboni & Dapretto, 2006; Rizzolatti et al., 2001; Rizzolatti & Craighero, 2004; Van Overwalle & Beatens, 2009).

The functionality of these networks is fundamental for social perception and social interaction and changes could negatively affect social functioning, as is the case in autism with regard to the MNS (Dapretto et al., 2005; Perkins, Stokes, McGillivray, & Bittar, 2010). In addition, impaired mentalizing abilities (i.e. ToM abilities) seem to be the best predictor of poor social competence in schizophrenia (Brüne, Abdel-Hamid, Lehmkämper, & Sonntag, 2007). Impaired social functioning is a core characteristic in schizophrenia (Frith, 1992) and deficits in ToM abilities were reported by almost all published ToM studies of schizophrenic patients (Bora, Yucel, & Pantelis, 2009a; Brüne, 2005; Corcoran, Mercer, & Frith, 1995; Harrington, Siegert, & McClure, 2005b; Sprong, Schothorst, Vos, Hox, & Van Engeland, 2007). Additionally, altered activity (mostly weaker) in the neural underpinnings was found in schizophrenia compared to healthy controls during ToM tasks (e.g., Brunet-Gouet & Decety, 2006; Russell et al., 2000; Brunet, Sarfati, Hardy-Baylé, & Decety, 2003; Walter et al., 2009; Brüne et al., 2008; Bara, Ciaramidaro, Walter, & Adenzato, 2011; Park et al., 2011). Like other social interaction tasks, processing of cooperation recruits the ToM network (Lissek et al., 2008), which is – as already mentioned – affected in patients with schizophrenia. However, until now cooperation is a form of social interaction that has received little attention in the research of schizophrenia even though it is the very basis of social existence. Moreover, perception of cooperation is a continuous social process for understanding social relations. In studies investigating the behavior in interactive games, it has been shown that patients violated rules of social exchange and showed altered cooperation behavior (reviewed in Wischniewski, Windmann, Juckel & Brüne, 2009). Motivated by this, we were interested in the basic neural processing of observed cooperation in patients.

Besides that, there are considerations implicating impaired ToM functioning with different dimensions of psychopathology. Patients with paranoid schizophrenia suffer from persecutory delusions, accompanied by feelings of being watched, followed, or that others secretly communicate with gestures (M. Startup & S. Startup, 2005). These feelings might be formed when patients make false inferences regarding the intentions of others (C.D. Frith & U. Frith, 1999). More specifically, it has been proposed that patients might tend to 'overmentalize' – this means that they mistakenly label actions as having more intention than is the case (Frith, 2004) – or exhibit 'hyper-theory of mind' (Abu-Akel, 1999). The role of impaired ToM in the formation of persecutory delusions has been discussed, but only a few empirical studies provided evidence for this relationship (reviewed in Blackwood, Howard, Bentall, & Murray, 2001; Chan & Chen, 2011; Harrington, Langdon, Siegert, & McClure, 2005a; Park et al., 2011). Consequently, more empirical research is needed to further investigate the possible relation between ToM deficits and delusions (Freeman, 2007).

Subclinical perceptual aberrations and experiences related to psychosis are present in the general healthy population (e.g., schizotypal traits) (Claridge, 1997; Stefanis et al., 2002). Moreover, schizotypy with particular positive subclinical symptoms (measured using a schizotypal personality questionnaire) is supposed to reflect the biological-genetic vulnerability for schizophrenia (Vollema, Sitskoorn, Appels, & Kahn, 2002). Furthermore, psychosis proneness, as indicated by schizotypal traits (Meyer & Hautzinger, 2002), is thought to be the subclinical expression of the same underlying biological factors of schizophrenia (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Besides reported behavioral ToM deficits in association with mainly positive dimensional symptoms (with unusual beliefs and aberrant perceptions) (Pickup, 2006), Modinos, Renken, Shamay-Tsoory, Ormel, and Aleman (2010) recently revealed evidence for altered prefrontal recruitment in people who are prone to psychosis.

The aim of the current study was to characterize the neural networks involved in the perception

of cooperative behavior using functional magnetic resonance imaging (fMRI). Therefore we constructed a non-interactive paradigm using video material that showed two cooperating actors in the context of object manipulation. Thus, the ecological validity of our paradigm is higher than in paradigms used in the majority of previous studies on social interaction (which for example used cartoons, animated geometric shapes, and verbal stories; e.g., Brunet, Sarfati, Hardy-Baylé, & Decety, 2000; Castelli, Happé, Frith, & Frith, 2000; Gallagher et al., 2000; Perner & Wimmer, 1985), the actions in our study were non-verbal, realistic, simple, and everyday actions. Furthermore, the paradigm is free of unnatural explicit instructions for retrospective attribution of mental states and of questions concerning the interaction. Comparable with real-life social situations subjects automatically infer the intentionality of others automatic and online in the presence of detailed information on biological motions. The concept of using real-life situations and differentiating them from more artificial explicit stimuli is supported by a recent study by Das, Lagopoulos, Coulston, Henderson, and Malhi (2012). They suggested a specific impairment in the automatic processing of mentalizing in schizophrenia. Thus, our hypotheses were that observation of cooperating actors recruits the MNS as well as the ToM network automatically, even without retrospective judgments of intentions. Furthermore, we hypothesized that this cooperation processing network shows a difference in neural activity – with weaker activity in schizophrenia compared to healthy controls during perception of cooperative behavior, and that these changes are related to delusional symptoms. To control for subclinical delusional experiences in healthy controls we took their cognitive-perceptional deficits into account.

Material and Methods

2.1 Participants

Nineteen patients (one female, 18 males; all right-handed) diagnosed with schizophrenia (without comorbid psychiatric disorders) according to DSM-IV criteria (American Psychiatric Association, 2000) by two independent psychiatrists using patient and relative interviews as well as past and present chart notes were included in the study. To ensure the absence of psychiatric disorders the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) was conducted. All participants were taking medication at the time of the study. Five patients were receiving typical neuroleptics and 14 atypical neuroleptics with a mean chlorpromazine equivalent dose (CPZ; Woods, 2003) of 745.6 mg (S.D. 500.8 mg) per day. Additionally, four patients were receiving SSRI medication. All patients were being treated as in-patients or were attending the day-clinic of the local departments of psychiatry and psychotherapy.

A total of 19 healthy controls (one female, 18 men; all right-handed) without a history of psychiatric disorders or first-degree relatives with psychotic illnesses took part in the study. Healthy controls were matched to the patient group on the basis of sex, age and education (see Table 1). All subjects were paid 30 Euros for participation and gave written informed consent. The study protocol was approved by the

Table 1: *Demographic and clinical characteristics of study participants*

	SCHIZ (n=19)	***CONTR (n=19)***	***Statistics***
Mean age (years)	30.0 ± 8.0	32.6 ± 8.7	n.s.
Male to female ratio	18:1	18:1	
Intelligence	107.1 ± 15.6	110.7 ± 16.1	n.s.
Mean duration of Illness (years)	8.0 ± 6.8	-	-
Mean CPZ equivalents (mg)	745.6 ± 500.8	-	-
SANS	23.1 ± 19.3	-	-
SAPS	18.9 ± 11.2	-	-

Patients with schizophrenia (SCHIZ); control subjects (CONTR); ± indicates the standard deviation; chlorpromazine equivalent dose (CPZ), Scale for the Assessment of Negative Symptoms (SANS); Scale for the Assessment of Positive Symptoms (SAPS)

local ethics committee according to the declaration of Helsinki.

2.2 Assessment instruments

All subjects responded to the 22 items of the self-report questionnaire SPQ-B (Schizotypal Personality Questionnaire-Brief; Raine & Benishay, 1995), a measure of psychosis proneness. This consists of three subscales that assess the degree to which an individual has schizophrenia-like cognitive-perceptual (magical thinking, unusual experiences, ideas of reference, paranoid ideation e.g. 'When shopping, do you get the feeling that other people are taking notice of you?'), interpersonal and disorganized features. In patients we assessed psychiatric symptoms using the Scales for the Assessment of Positive Symptoms (SAPS, Andreasen, 1984) and Negative Symptoms (SANS, Andreasen, 1983) in advance. Potential differences in the intelligence were estimated using a test for crystallized verbal intelligence (German vocabulary test, Multiple Choice Word Test, MWT-B) (Lehrl, Triebig, & Fischer, 1995). After the scanning procedure the "Reading the Mind in the Eyes'' test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) was assessed to clarify whether or not the ability to identify cognitive emotions - which requires inferences about others' beliefs or intentions (i.e. ToM abilities) - was given in all participants.

2.3 Stimulus construction

We used a set of 46 short video clips (cf. Leube et al., 2012). Videos were constructed for two different conditions: a) two persons manipulated everyday objects together (C+) and b) one person manipulated the same objects while the other was just watching (C-). The only difference between conditions was that in C+ the object was given to the main actor by the other actor, whereas in C- the main actor picked up the object himself (see Figure 1). All settings were kept as natural as possible, the whole upper part of the actors' bodies was visible and the head was not covered. All video clips lasted 8 s with at least 0.5 s delay before and after the onset and offset of action, respectively. The interaction between the actors took place after 1.0 s in videos in the C+ condition.

2.4 Experimental design and procedure

During the fMRI scanning procedure, videos were presented on an LCD screen using Presentation 11.0 software package (Neurobehavioral Systems, Albany, CA, USA, http://www.neurobs.com). Twenty-three videos of each of the two conditions were displayed in an event-related design. Every video was followed by a baseline condition (scrambled picture of the first video frame and a fixation cross) with a variable duration of 1.5–3.4 s. To avoid order artifacts, two different sets of pseudo randomized video sequences were generated. Subjects were instructed to watch the videos attentively and lie as relaxed and immobile as possible in the scanner. We did not highlight different conditions in order to leave the perception of cooperation rather automatic and thus more natural.

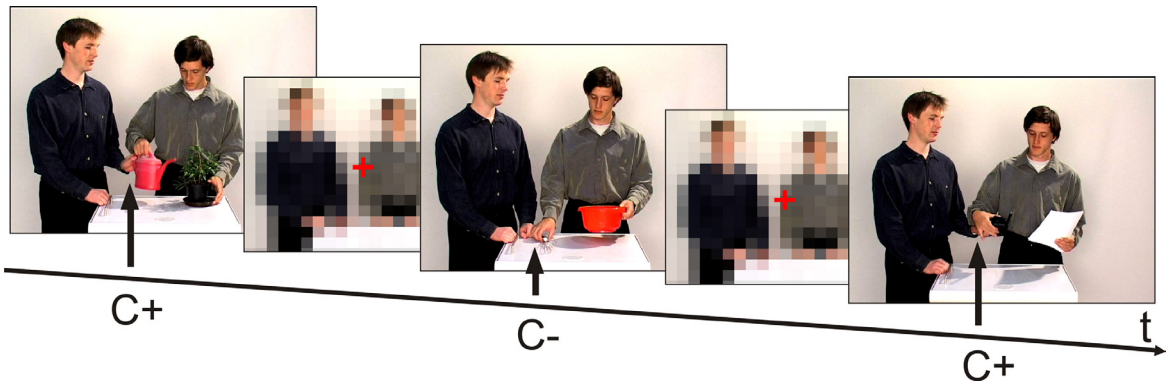

Figure 1.: Examples of stimulus material: *C+ with cooperation between the actors, C- without cooperation.*

2.5 FMRI data acquisition

Participants were scanned at 3T MR scanner (Siemens Trio, Erlangen, Germany) with 36 near-axial slices in ascending order and a distance factor of 10% providing whole brain coverage. An echo planar imaging (EPI) sequence was used for acquisition of 224 functional volumes during the experiment (repetition time = 2.19 s, echo time = 30 ms, flip angle = 90°, slice thickness = 3 mm, field of view = 192 mm, voxel resolution = 3 x 3 x 3 mm). After the functional run, an anatomical high-resolution T1-weighted 3-D scan was acquired (repetition time = 1.9 s, echo time = 2.52 ms, flip angle = 9°, slice thickness = 1 mm, field of view = 256 mm, voxel resolution = 1 x 1 mm, inter-slice gap = 0.5 mm).

2.6 Post-scan debriefing

Immediately after the scanning procedure participants were systematically debriefed. Participants were asked to distinguish objects they had seen in the video from those not being presented. A list of 20 words with 10 new items and 10 previously seen objects used by the actors in the videos was given to the subjects and they were asked to check boxes accordingly. The sum of correctly recognized items as either shown or not shown in the videos was used as a reference for attention to the videos. Before fMRI-measurement we did not point out that participants should infer the intention of the actors or that the actors cooperate in one kind of the videos. Therefore we checked for the perception of cooperation and asked whether they had detected a systematic difference between the videos and whether the cooperation between the actors was apparent to them. The first question gave additional information about whether the participants were aware of the two different conditions while watching the videos. If not, one can assume that the processing of the cooperation was rather automatic than explicit. The second question aimed at perception of cooperation in general.

2.7 FMRI data analysis

Functional MRI data were analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.5 (Mathworks Inc., Sherborn, Mass., USA). The first 8 volumes (dummy images) of the session were discarded from further analyses. At first the remaining scans and the 3D scan were manually assigned to the anterior commissure. To correct for head movement artifacts the functional images were realigned for each subject to the mean image and the resulting mean EPI image was co-registered with the high-resolution structural T1 image. Subsequently, images were segmented and the revealed parameters were used for spatial normalization to the standard stereotactic space defined by the Montreal Neurological Institute (MNI) template and resliced with a voxel size of 3×3×3 mm. Afterwards, they were spatially smoothed using an 10 mm full width at half maximum (FWHM, Mikl et al., 2008) isotropic Gaussian kernel to accommodate intersubject variation in brain anatomy, and high-pass filtered at 1/128 Hz to remove low frequency drifts.

For the analyses we used a fixed-effects General Linear Model at the single subject level including two regressors for the two conditions (C+, C-) convolved with the hemodynamic response function and the motion regressors. Time of onset for the regressors of interest was the beginning of the social cooperation within the C+ videos (1 s delay to the video onsets) and was synchronized for C- videos (i.e. in the condition without any cooperation the onset was 1 s after the beginning of the video). With regard to the short-lasting interaction in the videos, we modeled the regressors in an event related design with a duration of zero. Contrast images were calculated for activation in the condition with cooperation (C+) and for the condition without cooperation (C-) compared to the baseline activation (scrambled pictures). Furthermore, differential contrasts were calculated individually (C+>C-; C->C+).

In the following second-level random effects analysis, the individual contrast images (C+, C) were then entered into a 2x2 (group x condition) flexible factorial design to calculate interaction

effects using a non-directional F-test. Explanatory differential contrasts between subjects and tasks were calculated using separate t-tests in individual second-level designs – one-sample t-tests in the case of comparisons within a group (e.g., C+>C- in CONTR), two-sample t-tests in between group analyses (e.g., $C-_{SCHIZ}>C-_{CONTR}$) – in order to reveal differences in activation patterns. The locations of the activation maxima were reported as MNI-coordinates (Brett et al., 2002) and either family-wise error-corrected (FWE p<.05; in interaction analysis) or with the False Discovery Rate (FDR p<.05; in t-tests).

To determine the possible relations between activation patterns on the one hand and delusional symptoms in patients or psychosis proneness in controls on the other, we performed correlation analyses using SPSS 21.0 for Windows. More precisely, we analyzed the relationships between the first eigenvariate of the significantly differently activated clusters in patients and controls and the respective scores e.g. the cognitive-perceptual deficits subscale of the SPQ-B and the persecutory delusion item of the SAPS.

Results

3.1 Behavioral data

The post-scan debriefing revealed no significant difference in attention to the videos between healthy participants (CONTR) and patients with schizophrenia (SCHIZ). The number of correctly identified objects did not differ significantly between patients and controls (see Table 2). Additionally, all participants reported that they noticed the cooperation between the actors in the videos. Furthermore, 73.7% of the patient-group and 47.4% of the control-group did not detect the systematic difference between video conditions. Also, there were no group differences in the social-cognitive task. However, we found differences in the rating of all subscales of the SPQ-B.

3.2 Functional MRI

Interaction between condition and group

Most importantly, we found a significant effect of a group-by-condition interaction [($C+_{CONTR}$ versus $C-_{CONTR}$) versus ($C+_{SCHIZ}$ versus $C-_{SCHIZ}$)] in the medial and lateral prefrontal areas (left superior medial gyrus, bilateral superior frontal gyrus and left middle frontal gyrus, MFG), in the caudal part of the middle cingulate cortex (MCC, BA 23), and in the left angular gyrus (ANG, BA 39) (Table 3 and Figure 2). Contrast estimates (first eigenvariate) for the differently activated clusters of the interaction analysis indicated more activation for C+ in contrast to C- in the control group and the opposite activation pattern (C->C+) in the patient group (see bar graphs in Figure 2). As reported in the following sections, all areas identified in the interaction analysis were significantly more activated in separate differential contrasts (cf. supplementary Table 1).

Table 2: *Mean behavioral responses*

		SCHIZ	***CONTR***	***Statistics***
Reading the Mind Test (mean)		22.1 ± 5.54	23.2 ± 3.04	n.s.*
Correctly identified objects (mean) from a word list		17.4 ± 2.81	18.16 ± 1.64	n.s.*
SAPS	persecutory delusions	1.1 ± 1.2	-	-
SPQ-B	interpersonal deficits	4.7 ± 2.1	1.5 ± 1.6	p< 0.001
	cognitive-perceptual deficits	3.8 ± 1.8	0.6 ± 1.1	p< 0.001
	disorganization	2.6 ± 1.9	0.7 ± 1.1	p< 0.001

*Patients with schizophrenia (SCHIZ); control subjects (CONTR); Multiple Choice Word Test (MWT-B); ± indicates the standard deviation; Scale for the Assessment of Positive Symptoms (SAPS); Schizotypal Personality Questionnaire-Brief (SPQ-B); n.s. not significant, * t-tests comparison*

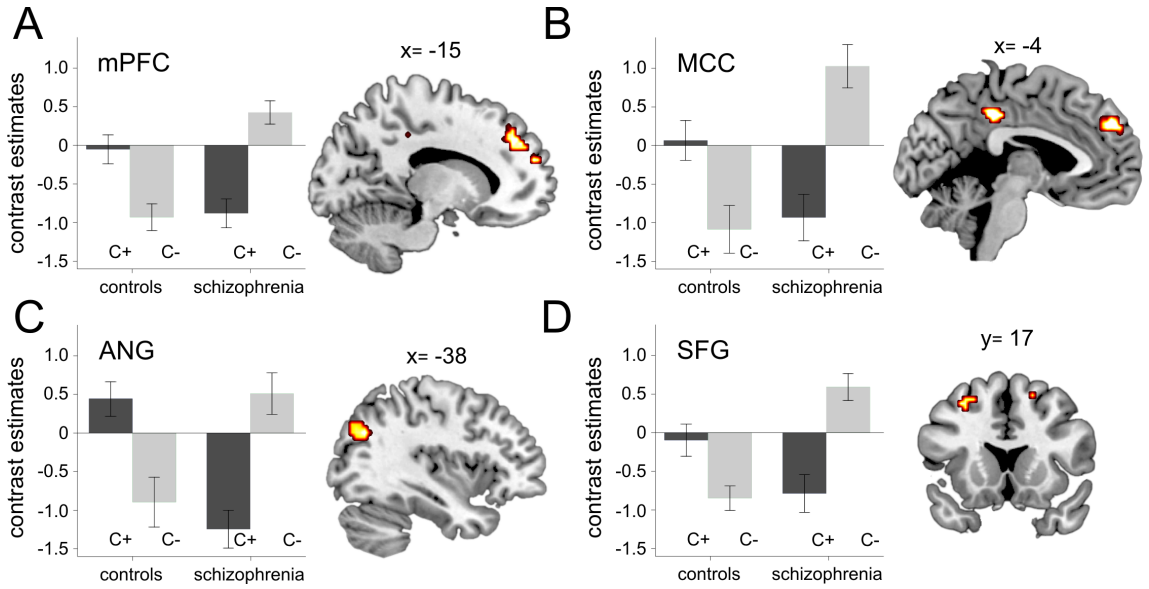

Figure 2.: Activated clusters of the interaction between group and condition *[F-Test: ($C+_{CONTR}$ versus $C-_{CONTR}$) versus ($C+_{SCHIZ}$ versus $C-_{SCHIZ}$)]. Bars show mean contrast estimates of significant clusters from **A** medial prefrontal cortex (mPFC), **B** caudal parts of the middle cingulate cortex (MCC), **C** angular gyrus (ANG), **D** superior frontal gyrus (SFG) (p< .05, FWE corr., extent threshold (k)=5, error bars indicate the standard error of the mean)*

Explanatory differential contrasts within groups

In healthy CONTR, the activation contrast between object manipulations with cooperation versus no cooperation (C+>C-, FDR corr. p<.05) revealed significantly higher activation in the bilateral temporo-parietal junction (TPJ), more precisely in the right superior temporal gyrus including the STS, the right and left middle temporal gyrus, the left IPL including the supramarginal gyrus (see Figure 3 and supplementary Table 1). Additionally, the left precuneus near the boarder to MCC, the left inferior frontal gyrus (IFG, BA 44) as well as parts of the medial prefrontal cortex (mPFC; e.g., right superior medial gyrus) were specifically active while watching two persons cooperatively manipulating objects together. We found no significant differences in the opposite contrast (C->C+) for CONTR (for separate baseline contrasts see

Table 3: *Statistical interaction [($C+_{CONTR}$ relative to $C-_{CONTR}$) relative to ($C+_{SCHIZ}$ relative to $C-_{SCHIZ}$)]*

Area	***MNI coordinates***			***Cluster size***	***z value***	***Voxel level p FWE corr. (peak voxel)***
	x	y	z			
Left Superior Medial Gyrus	-3	50	34	77	5.07	0.003
Left Superior Frontal Gyrus	-18	56	22		4.91	0.005
	-18	44	34		4.67	0.015
Left Middle Cingulate Cortex	-6	-31	40	40	4.95	0.004
Left Angular Gyrus	-42	-73	31	38	5.24	0.001
Left Middle Frontal Gyrus	-27	20	52	11	4.66	0.016
Right Superior Frontal Gyrus	18	20	55	5	4.43	0.04

F-Test; p< .05 FWE corr.; k=5; n_{SCHIZ}/n_{CONTR}=19/19

supplementary Table 2). However, in the latter contrast we found a significantly higher activation in the MCC, mPFC, left ANG, bilateral pSTS and middle temporal gyrus in SCHIZ. Other than in CONTR, in SCHIZ no significant differences in the specific contrast of cooperation versus no cooperation (C+>C-) were found. As a result of the nearly opposite activation patterns in SCHIZ and CONTR no main effect of task was obtained.

Explanatory differential contrasts between groups

The difference contrast between groups in the condition without cooperation ($C-_{SCHIZ}$>$C-_{CONTR}$, FDR corr., p<.05) revealed several differences in the activation pattern. Among other regions, SCHIZ patients showed higher activation in the bilateral cingulate cortex (including MCC), bilateral mPFC, in the TPJ (including right pSTS, ANG, and IPL) (Figure 3 C, for additional information see supplementary Table 1). In the condition with cooperation ($C+_{SCHIZ}$ versus $C+_{CONTR}$) the activation pattern of both groups did not differ significantly.

Correlations with psychopathology and psychosis proneness

Based on the potential relation between delusions and the findings of an altered activation pattern in SCHIZ, we paid special attention to the conspicuous increased activity in response to the C- condition. For further analysis we focused on the left ANG, mPFC and right pSTS clusters. We found that persecutory delusions (sub item SAPS Scale II No. 8) correlated positively with the angular (r=.45, p=.05), prefrontal (r=.54, p=.018) and pSTS (r=.48, p=.037) activity in response to C- in SCHIZ. The described activation pattern is neither significantly related to the duration of illness (all p's >.17) nor to medication (all p's >.57) or to the self-ratings of cognitive-perceptual deficits in patients (subscale SPQ-B; all p's >.28). In CONTR the activity in the angular and medial prefrontal cluster in response to C- correlated significantly with the cognitive-perceptual deficits (ANG: r=.46, p=.049; mPFC: r=.48, p=.04) but not in the case of pSTS activation (r=.28, p=.24).

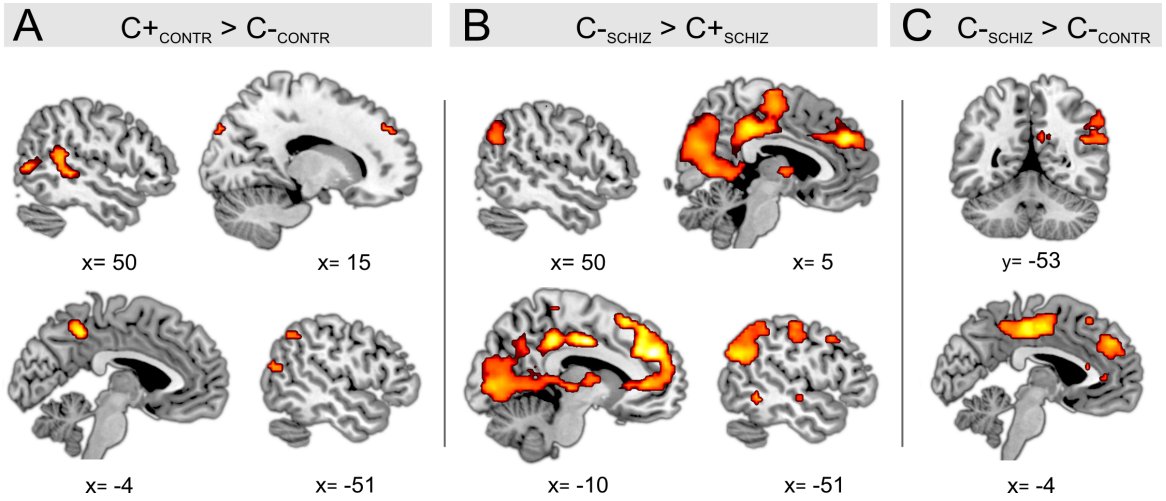

Figure 3.: *Brain areas that increase in activation when processing videos showing two persons with* ***A*** *cooperation (C+) versus non-cooperation (C-) in healthy controls (CONTR),* ***B*** *non-cooperation versus cooperation in patients with schizophrenia (SCHIZ), or* ***C*** *when contrasting brain activation as response to non-cooperation in SCHIZ versus CONTR (A/B one-sample and C two-sample random effects analyses, P< .05 false discovery rate (FDR) corr., k=5.*

Discussion

The primary goal of the current experiment was to determine possible neural differences in the perception of social interaction in patients with schizophrenia compared to a healthy control group. Five main results were obtained: (1) Perception of social interaction comprises co-activated MNS and ToM-related areas in healthy controls. (2) We found a roughly mirror-inverted activation pattern in the medial and lateral PFC, the MCC and the left ANG in patients with schizophrenia compared to controls. (3) Patients show hyperactivation in parts of the ToM network (e.g., pSTS, mPFC, ANG) during the non-social condition. (4) Furthermore, the altered activation pattern in pSTS, mPFC and ANG correlated with persecutory delusional symptoms in patients. (5) Even in healthy controls the activation in mPFC and ANG in response to the non-social condition was related to cognitive-perceptual deficits.

Network for perception of interactive behavior in healthy controls

At first we discuss the non-pathological neural network for perception of interactive behavior in healthy participants that comprises mirror neuron-associated regions (e.g., IPL, IFG) and ToM-related areas (mPFC, precuneus, TPJ including pSTS and ANG). Here, we provide further evidence for their co-activation in the perception of social cooperation as suggested by Becchio et al., (2012). Our results are consistent with those found by Leube et al., (2012), who used similar stimulus material on healthy participants. In contrast to their study, our optimized experimental design revealed significant differences in the direct comparison of two actors interacting versus two actors without interaction (differential contrast: C+>C-). Due to the higher recruitment of revealed regions and the almost identical constructed conditions, it is likely that these regions are particularly involved in the processing of cooperation between two persons in which manipulation of an object is the common goal.

Typically, social cooperation in healthy participants is studied with interactive games. Here we focused on passive observation of cooperation, but the neural correlates (mainly ToM-network and MNS), are concordant with those found in studies using interactive games or cartoon stories (cf. Decety, Jackson, Sommerville, Chaminade, & Meltzoff, 2004; Elliott, Völlm, Drury, McKie, Richardson, & Deakin, 2006; Emonds, Declerck, Boone, Vandervliet, & Parizel, 2012; Lissek et al., 2008; Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004). As described by Van Overwalle and Baetens (2009) one could imagine that in this context the more basal MNS interacts with the "mentalizing system" by providing intuitive input. Focusing on the functionality of this "mentalizing system", the TPJ, also known as the "social brain area" (Decety & Grèzes, 2006) and as a core region for moment-to-moment social interaction (Redcay et al., 2010), monitors the orientation of the perceived behavior in order to predict its likely goal (Van Overwalle, 2009). Likewise, the angular gyrus, as part of the TPJ, is known for its involvement in processing complex social information (e.g., immediate social interaction; reviewed in Wible, Preus, & Hashimoto, 2009) and its role in mentalizing tasks (see reviews in Decety & Lamm, 2007; Mar, 2011; Spreng, Mar, & Kim, 2009) – for example inferring intentions (Mason & Just, 2011). The mPFC, which has been implicated in theory of mind as well (C.D. Frith & U. Frith, 2006), seems to be important in reflective reasoning about actions and judgments, including goals and intentions (Van der Cruyssen, Van Duynslaeger, Cortoos, & Van Overwalle, 2009; Keysers & Gazzola, 2007), and decoupling mental states from their environment (Brunet-Gouet & Decety, 2006; Brüne, 2005). Another activated region, namely the precuneus, has been linked to processing the representation of complex goal contexts (Van Overwalle, 2009). In close agreement with our findings, the co-activation of the mPFC, precuneus, IFG, and STS during observation of videos with social interaction between actors was also reported by Iacoboni et al. (2004). With regard

to our study, perception of cooperation (C+>C-) seems to demand disentangling of actors' different roles in the performed action and more complex reasoning about their intentions. This higher requirement of aforementioned mentalizing processes in the cooperation condition compared to the condition without cooperation could be the reason for the specific activation of regions that have previously been shown to be associated with social cognition.

Differences between patients with schizophrenia and healthy controls

We found several differentially activated regions in the network for social interaction. It is notable that we found no differences in the post-scan debriefing (i.e. in the correctly identified objects on a wordlist). Based on this finding it is rather unlikely that the differences are due to attentional differences between groups.

Mirror-inverted activation pattern in schizophrenia

The interaction analysis comparing healthy controls and patients with schizophrenia showed altered activation patterns with regard to condition (C+/C-). More precisely, we found a roughly mirror-inverted deactivation and activation pattern of the lateral and medial PFC, caudal parts of the middle cingulate cortex (MCC) and the left ANG.

The role of the mPFC and the inferior parietal lobe (including the ANG) in producing the social cognitive deficits observed in schizophrenia has already been highlighted by Brunet-Gouet and Decety (2006), whereas the MCC has received little attention in literature, despite of its involvement in social exchange (e.g., Tomlin et al., 2006). In line with our findings, recruitment of the cingulate cortex, mPFC and TPJ were reported in several cooperation tasks in healthy participants (e.g., Brüne et al., 2011; Decety et al., 2004; Elliot et al., 2006; Lissek et al., 2008). Also, a higher recruitment of these areas (especially the mPFC) in healthy participants compared to patients has been observed previously in the context of ToM network investigations (e.g., Brunet et al., 2003; Lee et al., 2006). Interestingly, a comparable activation pattern in patients was found in a study regarding the processing of different intention types (Walter et al., 2009). Here the authors found a lack of deactivation in the mPFC and left TPJ in their control condition (non-intentional causal sequence of events concerning objects) and decreased activation/increased deactivation in all of the intention-loaded conditions in schizophrenia compared to controls.

The revealed interaction effect in our study can be explained best by the significant post-hoc t-test comparisons focusing on patients. Most importantly, in SCHIZ the cingulate cortex (including MCC), mPFC, in the TPJ (including right pSTS, ANG, and IPL) showed specifically increased activation in response to the condition without interaction (C-) compared to CONTR. Additionally, by comparing activation in SCHIZ between conditions (C->C+), we also found mPFC and TPJ (including right pSTS and left ANG) to be significantly more activated.

We should consider that the non-social condition (C-) is not a simple control task. It also requires reference to mental states, even though intentions must be interpreted to a lesser extent. In line with this, it has been suggested that the ToM mechanism is permanently online and constantly screens the mental states of people and even objects (Walter et al., 2009), which could make it prone to errors in some situations. We speculate that the non-social scenes (C-) elicit some ambiguity in patients and an overactivated mentalizing network (e.g., pSTS, mPFC, ANG) therefore reflects the enhanced processing of social cues, searching for intentionality or over-attributing of intentions to the actors. Besides its involvement in the observation of biological motion (Schultz, Friston, O'Doherty, Wolpert, & Frith, 2005), especially eye, hand and mouth movements (Allison, Puce, & McCarthy, 2000; C.D. Frith & U. Frith, 1999), the STS is presumed to be involved in the identification of intentionality and in attributing mental states to others (Blakemore & Decety, 2001; Pelphrey, Morris, & McCarthy,

2004; Perrett et al., 1989; Saxe & Wexler, 2005). Furthermore, it was depicted as a precursor for ToM by mentally imitating others' behavior through the mirroring of mental states of others (Gallese & Goldman, 1998). A recent meta-analysis revealed that the STS is rather less engaged during ToM tasks in patients with schizophrenia and autism (Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). In contrast to the stimulus material used in the studies referred to in this meta-analysis, we used more implicit stimuli, which may have induced a kind of ambiguity – which can also occur in real-life social situations – and which might have led to the overactivation of the STS in patients. Furthermore, hyperactivation of the STS (or TPJ) in social-cognitive control conditions in paranoid schizophrenia patients has been found by some authors (Mier, Sauer, Lis, Esslinger, Wilhelm, Gallhofer, & Kirsch, 2008; Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2008; Walter et al., 2009). All of these authors suggest a relationship between the STS hyperactivation and paranoid symptoms but none of them was able to demonstrate correlations with psychopathology. Moreover, it has been proposed that overactivation in the pSTS can produce misperceptions of intention and is involved in the formation of delusions (Wible, 2012; Wible et al., 2009). It has been argued that patients with paranoid symptoms exhibit hyper-intentionality, or "hyper-ToM", which means an overattribution of mental states and excessive formation of hypotheses regarding intentions (Abu-Akel & Bailey, 2000). Our data on patients with paranoid schizophrenia provide further evidence for this notion and besides confirming the role of the pSTS it additionally points to the involvement of the mPFC and the ANG in hyper-ToM. Furthermore, there is some prior experimental evidence for overmentalizing in patients with schizophrenia (Blakemore et al., 2003; Montag et al., 2011; Russell, Reynaud, Herba, Morris, & Corcoran, 2006; Walter et al., 2009).

Correlation with persecutory delusion

Despite findings of altered ToM processing in schizophrenia, it is unclear whether the alterations in functioning are associated with persecutory delusions. In the current study we show that the activation pattern in patients during action perception without interaction (C-) is correlated with persecutory delusions measured using the SAPS.

Suggestions about the role of ToM in the formation of paranoid delusions have a long history in the literature. It has long been assumed that altered processes of social inference (Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001; Frith, 1992) or abnormal causal attributions to social interactions (Bentall et al., 2001; Bentall, Kinderman, & Kaney, 1994; Kaney & Bentall, 1989) may play a role. More recently, some experimental evidence for a relation between the impairment of mentalizing and persecutory delusions was found (Blackwood et al., 2001; Harrington et al., 2005a; Park et al., 2011). In the first instance, our data support the suggestion of Wible et al., (2009), who proposed in their review that overactivation of the inferior parietal (including the ANG) and pSTS regions could result in several symptoms of schizophrenia such as incorrect attribution of intentions and the significance of others' actions.

A recent study showed that the perception of video material without conversation between two visible and independently-acting individuals can implicitly elicit self-referential perceptions, intention attribution, and anxiety, reflecting a paranoid response, which was more pronounced in patients (Park et al., 2011). It is conceivable that the same process took place when our patient group observed two actors without social interaction (C-). As already described in the previous section, with their hyperactive intention detector patients might perceive the observing actor suspiciously and overattribute any perceived intentions. This could explain the overactivation of the mPFC, ANG and pSTS and the correlation with persecutory delusion. In line with our reasoning that patients perceive the non-social condition (C-) as more ambiguous and the observed increased

activation of the mPFC, Jenkins and Mitchell (2010) demonstrated that under ambiguous inferences the mPFC shows increased activation compared to unambiguous mental state inferences. Together with our findings of an overactivated right pSTS in the condition without social interaction (C-), a structure that is known to perceive shifts in gaze (Pelphrey et al., 2004) and be neural biased towards threatening biological motion (Wheaton, Pipingas, Silberstein, & Puce, 2001), it is possible that patients may process the gaze direction of the watching actor in an abnormal threatening way. This is consistent with previous suggestions of selective attention to threat-related stimuli in schizophrenia (Bentall & Kaney, 1989; Fear, Sharp, & Healy, 1996), abnormal threat perception or "attentional bias" (e.g., Blackwood et al., 2001; Hall et al., 2008; Phillips, Senior, & David, 2000), and abnormal computation of gaze that may contribute to persecutory delusions (Hoffman, 2007). This is also in line with the hypothesis that an originally neutral situation could be recognized as threatening due to increased activity in parts of the TPJ/IP/STS that are responsible for fear processing (Wible, 2012; Wible et al., 2009). Taken together, our data provide novel experimental evidence for the existing theoretical assumption that increased activity in ToM-related areas (predominantly pSTS, ANG and mPFC) may play an important role particularly in the formation of persecutory delusions and could lead to misinterpretations while perceiving social interaction.

Psychosis proneness and altered activation in healthy controls

We collected self-ratings of cognitive-perceptual deficits for healthy controls and examined a possible association with their observed activity pattern. We found that the higher the schizotypy scores the higher the activation in the non-social condition (C-) in the current clusters of the ANG and mPFC. This suggests that subjects with high schizotypy scores might recruit their network in the non-social scene (C-) in a more similar way to patients than subjects with low schizotypy scores. Hence, possibly related over-intentionality may reflect a trait-like deficit, increasing the risk for schizophrenia (see Bora, Yücel, & Pantelis, 2009b; Brüne, 2005; Penn, Sanna, & Roberts, 2008). Recent behavioral studies have pointed at poorer performance in ToM tasks – mostly written or picture stories or the Reading the Mind in the Eyes task – in healthy individuals with schizotypal characteristics (Langdon & Coltheart, 1999, 2004; Meyer & Shean, 2006; Pickup, 2006) and even in high-risk relatives (Irani et al., 2006; Marjoram et al., 2006b). Also, our data are consistent with previous neuroimaging results showing that individuals who scored high in psychosis proneness showed greater activation of prefrontal areas during mentalizing than those with low scores (Modinos et al., 2010). Similar results were observed for high-risk relatives compared to controls (Marjoram et al., 2006a). We improved these findings by using naturalistic stimuli without explicitly asking for mental state attribution and by suggesting a possible role of the ANG. And contrary to these authors, who interpreted the higher activation in prefrontal regions as a compensatory mechanism in order to achieve adequate ToM functioning, we propose that it could reflect a tendency to overmentalizing. These findings are of great importance for an understanding of the relation between attributional bias during ToM and the formation of persecutory delusions.

Limitations

This study has some limitations that should be addressed. At first, all patients received medication. However, the performed correlation analysis with the first eigenvariate of studied clusters and the medication revealed that there is no effect of medication on the activation pattern in respective brain regions. Second, in contrast to healthy subjects, we found no relation of schizotypy scores and activation pattern in patients. This might be due to the fact that the reliability and validity of the SPQ-B was assessed in nonclinical populations or patients with schizotypal personality disorder (e.g.,

Fonseca-Pedrero, Paíno-Piñeiro, Lemos-Giráldez, Villazón-García, & Muñiz, 2009; Raine & Benishay, 1995) or in heterogeneous inpatient populations with mixed support (Axelrod, Grilo, Sanislow, & McGlashan, 2001). However, it is not clear whether this scale is appropriate for patients with paranoid schizophrenia who suffer from excessive cognitive-perceptual deficits of clinical relevance. Anyway, the persecutory delusion subitem of the well-established SAPS correlated with the activation and provides an adequate explanation for the hyperactivation in patients in response to the non-cooperative condition. Third, it has to be noted that additional 25 percent of CONTR (compared to SCHIZ) were explicitly aware of the different conditions. Therefore, it might be possible that CONTR have paid more attention to the different conditions aiming at discovering the aim of the study.

Conclusion

To conclude, we have shown that the network for perception of cooperative and non-cooperative behavior is altered in paranoid schizophrenia in a mirror-inverted way. In schizophrenic patients the prefrontal-parietal network showed a trend towards attenuation in response to the cooperative context, but was significantly increased in the non-cooperative context compared to controls. Furthermore, the latter finding was associated with delusions in patients. The more severe the delusional symptomatology the higher was the activation in the mPFC, ANG and pSTS during perception of non-cooperative behavior. Hereby we provide novel experimental evidence for the idea of an overactivated ToM network in patients, which might reflect overmentalizing. This could be attributed to ambiguous perception of the non-cooperative scenes resulting from a constantly hyperactive intention detector and the patients' abnormal threat perception (e.g., abnormal computation of gaze). A tendency to overmentalizing was even present in healthy participants with subclinical schizotypal cognitive-perceptual deficits. Therefore, our study supports the assumption that the ToM network (especially mPFC, ANG and pSTS) plays an important role in the formation of delusions.

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References

Abu-Akel, A., & Bailey, A.L. (2000). The possibility of different forms of theory of mind impairment in psychiatric and developmental disorders. Psychological medicine, 30(3), 735–8.

Abu-Akel, A. (1999). Impaired theory of mind in schizophrenia. Pragmatics & Cognition, 7(2), 247–282. doi:10.1075/pc.7.2.02abu

Allison, T., Puce, A., & McCarthy, G. (2000). Social perception from visual cues: role of the STS region. Trends in cognitive sciences, 4(7), 267–278. doi:10.1016/S1364-6613(00)01501-1

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders. (4th ed.). Washington DC: American Psychiatric Association.

Amodio, D.M., & Frith, C.D. (2006). Meeting of minds: the medial frontal cortex and social cognition. Nature reviews. Neuroscience, 7(4), 268–77. doi:10.1038/nrn1884

Andreasen, N.C. (1983). Scale for the Assessment of Negative Symptoms (SANS). Iowa City, IA : University of Iowa.

Andreasen, N.C. (1984). Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA : University of Iowa.

Axelrod, S.R., Grilo, C.M., Sanislow, C., & McGlashan, T.H. (2001). Schizotypal Personality Questionnaire-Brief: Factor Structure and Convergent Validity in Inpatient Adolescents. Journal of Personality Disorders, 15(2), 168–179. doi:10.1521/pedi.15.2.168.19219

Bara, B.G., Ciaramidaro, A., Walter, H., & Adenzato, M. (2011). Intentional Minds: A

Philosophical Analysis of Intention Tested through fMRI Experiments Involving People with Schizophrenia, People with Autism, and Healthy Individuals. Frontiers in human neuroscience, 5, 7. doi:10.3389/fnhum.2011.00007

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. Journal of child psychology and psychiatry, and allied disciplines, 42(2), 241–51. doi: 10.1111/1469-7610.00715

Baron-Cohen, S. (1995). Mindblindness: An Essay on Autism and Theory of Mind. Boston: MIT Press/Bradford Books.

Becchio, C., Cavallo, A., Begliomini, C., Sartori, L., Feltrin, G., & Castiello, U. (2012). Social grasping: from mirroring to mentalizing. NeuroImage, 61(1), 240–8. doi:10.1016/j.neuroimage.2012.03.013

Bentall, R.P., Corcoran, R., Howard, R., Blackwood, N., & Kinderman, P. (2001). Persecutory delusions: a review and theoretical integration. Clinical psychology review, 21(8), 1143–92. doi:10.1016/S0272-7358(01)00106-4

Bentall, R.P., & Kaney, S. (1989). Content specific information processing and persecutory delusions: an investigation using the emotional Stroop test. The British journal of medical psychology, 62 (Pt 4), 355–64. doi:10.1111/j.2044-8341.1989.tb02845.x

Bentall, R.P., Kinderman, P., & Kaney, S. (1994). The self, attributional processes and abnormal beliefs: towards a model of persecutory delusions. Behaviour research and therapy, 32(3), 331–41. doi: 10.1016/0005-7967(94)90131-7

Blackwood, N.J., Howard, R.J., Bentall, R.P., & Murray, R.M. (2001). Cognitive neuropsychiatric models of persecutory delusions. The American journal of psychiatry, 158(4), 527–39. doi: 10.1176/appi.ajp.158.4.527

Blakemore, S.J., & Decety, J. (2001). From the perception of action to the understanding of intention. Nature reviews. Neuroscience, 2(8), 561–7. doi:10.1038/35086023

Blakemore, S.J., Boyer, P., Pachot-Clouard, M., Meltzoff, A., Segebarth, C., & Decety, J. (2003). The detection of contingency and animacy from simple animations in the human brain. Cerebral cortex, 13(8), 837–44. doi: 10.1093/cercor/13.8.837

Bora, E., Yücel, M., & Pantelis, C. (2009). Theory of mind impairment: a distinct trait-marker for schizophrenia spectrum disorders and bipolar disorder? Acta psychiatrica Scandinavica, 120(4), 253–64. doi:10.1111/j.1600-0447.2009.01414.x

Bora, E., Yucel, M., & Pantelis, C. (2009). Theory of mind impairment in schizophrenia: meta-analysis. Schizophrenia research, 109(1-3), 1–9. doi:10.1016/j.schres.2008.12.020

Brett, M., Johnsrude, I.S., & Owen, A.M. (2002). The problem of functional localization in the human brain. Nature reviews. Neuroscience, 3(3), 243–9. doi:10.1038/nrn756

Brunet, E., Sarfati, Y., Hardy-Baylé, M.C., & Decety, J. (2000). A PET investigation of the attribution of intentions with a nonverbal task. NeuroImage, 11(2), 157–66. doi:10.1006/nimg.1999.0525

Brunet, E., Sarfati, Y., Hardy-Baylé, M.-C., & Decety, J. (2003). Abnormalities of brain function during a nonverbal theory of mind task in schizophrenia. Neuropsychologia, 41(12), 1574–82. doi: 10.1016/S0028-3932(03)00119-2

Brunet-Gouet, E., & Decety, J. (2006). Social brain dysfunctions in schizophrenia: a review of neuroimaging studies. Psychiatry research, 148(2-3), 75–92. doi:10.1016/j.pscychresns.2006.05.001

Brüne, M. (2005). "Theory of mind" in schizophrenia: a review of the literature. Schizophrenia bulletin, 31(1), 21–42. doi:10.1093/schbul/sbi002

Brüne, M., Abdel-Hamid, M., Lehmkämper, C., & Sonntag, C. (2007). Mental state attribution, neurocognitive functioning, and psychopathology: what predicts poor social competence in schizophrenia best? Schizophrenia research, 92(1-3), 151–9. doi:10.1016/j.schres.2007.01.006

Brüne, M., Lissek, S., Fuchs, N., Witthaus, H., Peters, S., Nicolas, V., Juckel, G., et al. (2008). An fMRI study of theory of mind in schizophrenic patients with "passivity" symptoms. Neuropsychologia, 46(7), 1992–2001. doi:10.1016/j.neuropsychologia.2008.01.023

Brüne, M., Ozgürdal, S., Ansorge, N., Von Reventlow, H. G., Peters, S., Nicolas, V., Tegenthoff, M., et al. (2011). An fMRI study of "theory of mind" in at-risk states of psychosis: comparison with manifest schizophrenia and healthy controls. NeuroImage, 55(1), 329–37. doi:10.1016/j.neuroimage.2010.12.018

Calarge, C., Andreasen, N.C., & O'Leary, D.S. (2003). Visualizing how one brain understands another: a PET study of theory of mind. The American journal of psychiatry, 160(11), 1954–64. doi: 10.1176/appi.ajp.160.11.1954

Carr, L., Iacoboni, M., Dubeau, M.-C., Mazziotta, J.C., & Lenzi, G.L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proceedings of the National Academy of Sciences of the United States of America, 100(9), 5497–502. doi:10.1073/pnas.0935845100

Castelli, F., Happé, F., Frith, U., & Frith, C. (2000). Movement and mind: a functional imaging study of perception and interpretation of complex intentional movement patterns. NeuroImage, 12(3), 314–25. doi:10.1006/nimg.2000.0612

Cavanna, A.E., & Trimble, M.R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. Brain : a journal of neurology, 129(Pt 3), 564–83. doi:10.1093/brain/awl004

Chan, K.K.S., & Chen, E.Y.H. (2011). Theory of mind and paranoia in schizophrenia: a game theoretical investigation framework. Cognitive neuropsychiatry, 16(6), 505–29. doi:10.1080/13546805.2011.561576

Ciaramidaro, A., Adenzato, M., Enrici, I., Erk, S., Pia, L., Bara, B.G., & Walter, H. (2007). The intentional network: how the brain reads varieties of intentions. Neuropsychologia, 45(13), 3105–13. doi:10.1016/j.neuropsychologia.2007.05.011

Claridge, G. (1997). Schizotypy: Implications for illness and health. (G. Claridge, Ed.) (p. xii 340 pp.). Oxford: Oxford University Press.

Corcoran, R., Mercer, G., & Frith, C.D. (1995). Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. Schizophrenia research, 17(1), 5–13. doi:10.1016/0920-9964(95)00024-G

Dapretto, M., Davies, M.S., Pfeifer, J.H., Scott, A.A., Sigman, M., Bookheimer, S.Y., & Iacoboni, M. (2005). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. Nature neuroscience, 9(1), 28–30. doi:10.1038/nn1611

Das, P., Lagopoulos, J., Coulston, C.M., Henderson, A.F., & Malhi, G.S. (2012). Mentalizing impairment in schizophrenia: a functional MRI study. Schizophrenia research, 134(2-3), 158–64. doi:10.1016/j.schres.2011.08.019

Decety, J., & Grèzes, J. (2006). The power of simulation: imagining one's own and other's behavior. Brain research, 1079(1), 4–14. doi:10.1016/j.brainres.2005.12.115

Decety, J., Jackson, P. L., Sommerville, J. A., Chaminade, T., & Meltzoff, A. N. (2004). The neural bases of cooperation and competition: an fMRI investigation. NeuroImage, 23(2), 744–51. doi:10.1016/j.neuroimage.2004.05.025

Decety, J., & Lamm, C. (2007). The role of the right temporoparietal junction in social interaction: how low-level computational processes contribute to meta-cognition. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry, 13(6), 580–93. doi:10.1177/1073858407304654

Elliott, R., Völlm, B., Drury, A., McKie, S., Richardson, P., & Deakin, J. F. W. (2006). Co-operation with another player in a financially rewarded guessing game activates regions implicated in theory of mind. Social neuroscience, 1(3-4), 385–95. doi:10.1080/17470910601041358

Emonds, G., Declerck, C. H., Boone, C., Vandervliet, E. J. M., & Parizel, P. M. (2012). The cognitive demands on cooperation in social dilemmas: an fMRI study. Social neuroscience, 7(5), 494–509. doi:10.1080/17470919.2012.655426

Fabbri-Destro, M., & Rizzolatti, G. (2008). Mirror neurons and mirror systems in monkeys and humans. Physiology, 23, 171–9. doi:10.1152/physiol.00004.2008

Fear, C., Sharp, H., & Healy, D. (1996). Cognitive processes in delusional disorders. The British journal of psychiatry: the journal of mental science, 168(1), 61–7. doi: 10.1192/bjp.168.1.61

Fonseca-Pedrero, E., Paíno-Piñeiro, M. D. L. M., Lemos-Giráldez, S., Villazón-García, U., & Muñiz, J. (2009). Validation of the Schizotypal Personality Questionnaire—Brief Form in adolescents. Schizophrenia Research, 111(1), 53-60. doi: 10.1016/j.schres.2009.03.006

Freeman, D. (2007). Suspicious minds: the psychology of persecutory delusions. Clinical psychology review, 27(4), 425–57. doi:10.1016/j.cpr.2006.10.004

Frith, C.D., & Frith, U. (1999). Interacting minds--a biological basis. Science, 286(5445), 1692–5. doi: 10.1126/science.286.5445.1692

Frith, C.D. (2004). Schizophrenia and theory of mind. Psychological Medicine, 34(03), 385–389. doi:10.1017/S0033291703001326

Frith, C.D., & Frith, U. (2006). The neural basis of mentalizing. Neuron, 50(4), 531–4. doi:10.1016/j.neuron.2006.05.001

Frith, C.D. (1992). The cognitive neuropsychology of schizophrenia. (N. Hillsdale, Ed.) (p. xiv 169 pp.). UK: Psychology Press.

Frith, U., & Frith, C.D. (2003). Development and neurophysiology of mentalizing. Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 358(1431), 459–73. doi:10.1098/rstb.2002.1218

Gallagher, H.L., Happé, F., Brunswick, N., Fletcher, P.C., Frith, U., & Frith, C.D. (2000). Reading the mind in cartoons and stories: an fMRI study of "theory of mind" in verbal and nonverbal tasks. Neuropsychologia, 38(1), 11–21. doi: 10.1016/S0028-3932(99)00053-6

Gallese, V., & Goldman, A. (1998). Mirror neurons and the simulation theory of mind-reading. Trends in cognitive sciences, 2(12), 493–501. doi: 10.1016/S1364-6613(98)01262-5

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. Brain, 119(2), 593–609. doi:10.1093/brain/119.2.593

Hall, J., Whalley, H.C., McKirdy, J.W., Romaniuk, L., McGonigle, D., McIntosh, A.M., Baig, B. J., et al. (2008). Overactivation of fear systems to neutral faces in schizophrenia. Biological psychiatry, 64(1), 70–3. doi:10.1016/j.biopsych.2007.12.014

Harrington, L., Langdon, R., Siegert, R.J., & McClure, J. (2005). Schizophrenia, theory of mind, and persecutory delusions. Cognitive neuropsychiatry, 10(2), 87–104. doi:10.1080/13546800344000327

Harrington, L., Siegert, R.J., & McClure, J. (2005). Theory of mind in schizophrenia: a critical review. Cognitive neuropsychiatry, 10(4), 249–86. doi:10.1080/13546800444000056

Hoffman, R.E. (2007). A social deafferentation hypothesis for induction of active schizophrenia. Schizophrenia bulletin, 33(5), 1066–70. doi:10.1093/schbul/sbm079

Iacoboni, M., & Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. Nature reviews. Neuroscience, 7(12), 942–51. doi:10.1038/nrn2024

Iacoboni, M., Lieberman, M.D., Knowlton, B.J., Molnar-Szakacs, I., Moritz, M., Throop, C. J., & Fiske, A.P. (2004). Watching social interactions produces dorsomedial prefrontal and medial parietal BOLD fMRI signal increases compared to a resting baseline. NeuroImage, 21(3), 1167–73. doi:10.1016/j.neuroimage.2003.11.013

Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J.C., & Rizzolatti, G. (2005). Grasping the intentions of others with one's own mirror neuron system. PLoS biology, 3(3), e79. doi:10.1371/journal.pbio.0030079

Irani, F., Platek, S.M., Panyavin, I.S., Calkins, M.E., Kohler, C., Siegel, S.J., Schachter, M., et al. (2006). Self-face recognition and theory of mind in patients with schizophrenia and first-degree relatives. Schizophrenia research, 88(1-3), 151–60. doi:10.1016/j.schres.2006.07.016

Jenkins, A.C., & Mitchell, J.P. (2010). Mentalizing under uncertainty: dissociated neural responses to ambiguous and unambiguous mental state inferences. Cerebral cortex (New York, N.Y. : 1991), 20(2), 404–10. doi:10.1093/cercor/bhp109

Kaney, S., & Bentall, R.P. (1989). Persecutory delusions and attributional style. The British journal of medical psychology, 62 (Pt 2), 191–8. doi:10.1111/j.2044-8341.1989.tb02826.x

Keysers, C., & Gazzola, V. (2007). Integrating simulation and theory of mind: from self to social cognition. Trends in cognitive sciences, 11(5), 194–6. doi:10.1016/j.tics.2007.02.002

Langdon, R., & Coltheart, M. (2004). Recognition of metaphor and irony in young adults: the impact of schizotypal personality traits. Psychiatry research, 125(1), 9–20. doi:10.1016/j.psychres.2003.10.005

Lee, K.-H., Brown, W.H., Egleston, P.N., Green, R.D.J., Farrow, T.F.D., Hunter, M.D., Parks, R.W., et al. (2006). A functional magnetic resonance imaging study of social cognition in schizophrenia during an acute episode and after recovery. The American journal of psychiatry, 163(11), 1926–33. doi:10.1176/appi.ajp.163.11.1926

Lehrl, S., Triebig, G., & Fischer, B. (1995). Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurologica Scandinavica, 91(5), 335–345. doi:10.1111/j.1600-0404.1995.tb07018.x

Leube, D., Straube, B., Green, A., Blümel, I., Prinz, S., Schlotterbeck, P., & Kircher, T. (2012). A possible brain network for representation of cooperative behavior and its implications for the psychopathology of schizophrenia. Neuropsychobiology, 66(1), 24–32. doi:10.1159/000337131

Lissek, S., Peters, S., Fuchs, N., Witthaus, H., Nicolas, V., Tegenthoff, M., Juckel, G., et al. (2008). Cooperation and deception recruit different subsets of the theory-of-mind network. PloS one, 3(4), e2023. doi:10.1371/journal.pone.0002023

Mar, R.A. (2011). The neural bases of social cognition and story comprehension. Annual review of psychology, 62, 103–34. doi:10.1146/annurev-psych-120709-145406

Marjoram, D., Job, D.E., Whalley, H.C., Gountouna, V.-E., McIntosh, A.M., Simonotto, E., Cunningham-Owens, D., et al. (2006). A visual joke fMRI investigation into Theory of Mind and enhanced risk of schizophrenia.

NeuroImage, 31(4), 1850–8. doi:10.1016/j.neuroimage.2006.02.011

Marjoram, D., Miller, P., McIntosh, A.M., Cunningham Owens, D.G., Johnstone, E.C., & Lawrie, S. (2006). A neuropsychological investigation into "Theory of Mind" and enhanced risk of schizophrenia. Psychiatry research, 144(1), 29–37. doi:10.1016/j.psychres.2006.01.008

Mason, R.A., & Just, M.A. (2011). Differentiable cortical networks for inferences concerning people's intentions versus physical causality. Human brain mapping, 32(2), 313–29. doi:10.1002/hbm.21021

Meyer, J., & Shean, G. (2006). Social-cognitive functioning and schizotypal characteristics. The Journal of psychology, 140(3), 199–207. doi:10.3200/JRLP.140.3.199-207

Meyer, T.D., & Hautzinger, M. (2002). Prediction of personality disorder traits by psychosis proneness scales in a German sample of young adults. Journal of clinical psychology, 58(9), 1091–101. doi:10.1002/jclp.10040

Mier, D., Sauer, C., Lis, S., Esslinger, C., Wilhelm, J., Gallhofer, B., & Kirsch, P. (2010). Neuronal correlates of affective theory of mind in schizophrenia out-patients: evidence for a baseline deficit. Psychological Medicine, 40(10), 1607–1617. doi: 10.1017/S0033291709992133

Mikl, M., Marecek, R., Hlustík, P., Pavlicová, M., Drastich, A., Chlebus, P., Brázdil, M., et al. (2008). Effects of spatial smoothing on fMRI group inferences. Magnetic resonance imaging, 26(4), 490–503. doi:10.1016/j.mri.2007.08.006

Modinos, G., Renken, R., Shamay-Tsoory, S.G., Ormel, J., & Aleman, A. (2010). Neurobiological correlates of theory of mind in psychosis proneness. Neuropsychologia, 48(13), 3715–24. doi:10.1016/j.neuropsychologia.2010.09.030

Montag, C., Dziobek, I., Richter, I. S., Neuhaus, K., Lehmann, A., Sylla, R., Heekeren, H.R., et al. (2011). Different aspects of theory of mind in paranoid schizophrenia: evidence from a video-based assessment. Psychiatry research, 186(2-3), 203–9. doi:10.1016/j.psychres.2010.09.006

Mukamel, R., Ekstrom, A.D., Kaplan, J., Iacoboni, M., & Fried, I. (2010). Single-neuron responses in humans during execution and observation of actions. Current biology : CB, 20(8), 750–6. doi:10.1016/j.cub.2010.02.045

Park, I.H., Ku, J., Lee, H., Kim, S.Y., Kim, S.I., Yoon, K.J., & Kim, J.-J. (2011). Disrupted theory of mind network processing in response to idea of reference evocation in schizophrenia. Acta psychiatrica Scandinavica, 123(1), 43–54. doi:10.1111/j.1600-0447.2010.01597.x

Pelphrey, K.A., Morris, J.P., & McCarthy, G. (2004). Grasping the intentions of others: the perceived intentionality of an action influences activity in the superior temporal sulcus during social perception. Journal of cognitive neuroscience, 16(10), 1706–16. doi:10.1162/0898929042947900

Penn, D.L., Sanna, L.J., & Roberts, D.L. (2008). Social cognition in schizophrenia: an overview. Schizophrenia bulletin, 34(3), 408–11. doi:10.1093/schbul/sbn014

Perkins, T., Stokes, M., McGillivray, J., & Bittar, R. (2010). Mirror neuron dysfunction in autism spectrum disorders. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia, 17(10), 1239–43. doi:10.1016/j.jocn.2010.01.026

Perner, J., & Wimmer, H. (1985). "John thinks that Mary thinks that…" attribution of second-order beliefs by 5- to 10-year-old children. Journal of Experimental Child Psychology, 39(3), 437–471. doi:10.1016/0022-0965(85)90051-7

Perrett, D.I., Harries, M.H., Bevan, R., Thomas, S., Benson, P.J., Mistlin, A.J., Chitty, A.J., et al. (1989). Frameworks of analysis for the neural representation of animate objects and actions. The Journal of experimental biology, 146, 87–113.

Phillips, M.L., Senior, C., & David, A.S. (2000). Perception of threat in schizophrenics with persecutory delusions: an investigation using visual scan paths. Psychological medicine, 30(1), 157–67. doi:10.1017/S0033291799001397

Pickup, G.J. (2006). Theory of mind and its relation to schizotypy. Cognitive neuropsychiatry, 11(2), 177–92. doi:10.1080/13546800444000236

Pinkham, A.E., Hopfinger, J.B., Pelphrey, K.A., Piven, J., & Penn, D.L. (2008). Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. Schizophrenia research, 99(1-3), 164–75. doi:10.1016/j.schres.2007.10.024

Premack, D., & Woodruff, G. (1978). Does the chimpanzee have a theory of mind? Behavioral and Brain Sciences, 1(04), 515–526. doi:10.1017/S0140525X00076512

Raine, A., & Benishay, D. (1995). The SPQ-B: A Brief Screening Instrument for Schizotypal Personality Disorder. Journal of Personality Disorders, 9(4), 346–355. doi:10.1521/pedi.1995.9.4.346

Redcay, E., Dodell-Feder, D., Pearrow, M.J., Mavros, P.L., Kleiner, M., Gabrieli, J.D.E., & Saxe, R. (2010). Live face-to-face interaction during fMRI: a new tool for social cognitive neuroscience. NeuroImage, 50(4), 1639–47. doi:10.1016/j.neuroimage.2010.01.052

Rilling, J.K., Sanfey, A. G., Aronson, J. A., Nystrom, L. E., & Cohen, J. D. (2004). The neural correlates of theory of mind within interpersonal interactions. NeuroImage, 22(4), 1694–703. doi:10.1016/j.neuroimage.2004.04.015

Rizzolatti, G., Fogassi, L., & Gallese, V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. Nature reviews. Neuroscience, 2(9), 661–70. doi:10.1038/35090060

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. Annual review of neuroscience, 27, 169–92. doi:10.1146/annurev.neuro.27.070203.144230

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. Cognitive Brain Research, 3(2), 131–141. doi:10.1016/0926-6410(95)00038-0

Russell, T.A., Rubia, K., Bullmore, E.T., Soni, W., Suckling, J., Brammer, M.J., Simmons, A., et al. (2000). Exploring the social brain in schizophrenia: left prefrontal underactivation during mental state attribution. The American journal of psychiatry, 157(12), 2040–2. doi:10.1176/appi.ajp.157.12.2040

Russell, T.A., Reynaud, E., Herba, C., Morris, R., & Corcoran, R. (2006). Do you see what I see? Interpretations of intentional movement in schizophrenia. Schizophrenia research, 81(1), 101–11. doi:10.1016/j.schres.2005.10.002

Saxe, R. (2006). Uniquely human social cognition. Current opinion in neurobiology, 16(2), 235–9. doi:10.1016/j.conb.2006.03.001

Saxe, R., & Wexler, A. (2005). Making sense of another mind: the role of the right temporo-parietal junction. Neuropsychologia, 43(10), 1391–9. doi:10.1016/j.neuropsychologia.2005.02.013

Schultz, J., Friston, K.J., O'Doherty, J., Wolpert, D.M., & Frith, C.D. (2005). Activation in posterior superior temporal sulcus parallels parameter inducing the percept of animacy. Neuron, 45(4), 625–35. doi:10.1016/j.neuron.2004.12.052

Seghier, M.L. (2012). The Angular Gyrus: Multiple Functions and Multiple Subdivisions. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry, 19(1), 43–61. doi:10.1177/1073858412440596

Sperduti, M., Delaveau, P., Fossati, P., & Nadel, J. (2011). Different brain structures related to self- and external-agency attribution: a brief review and meta-analysis. Brain structure & function, 216(2), 151–7. doi:10.1007/s00429-010-0298-1

Spreng, R.N., Mar, R.A., & Kim, A.S.N. (2009). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. Journal of cognitive neuroscience, 21(3), 489–510. doi:10.1162/jocn.2008.21029

Sprong, M., Schothorst, P., Vos, E., Hox, J., & Van Engeland, H. (2007). Theory of mind in schizophrenia: meta-analysis. The British journal of psychiatry : the journal of mental science, 191, 5–13. doi:10.1192/bjp.bp.107.035899

Startup, M., & Startup, S. (2005). On two kinds of delusion of reference. Psychiatry research, 137(1-2), 87–92. doi:10.1016/j.psychres.2005.07.007

Stefanis, N.C., Hanssen, M., Smirnis, N.K., Avramopoulos, D.A., Evdokimidis, I.K., Stefanis, C.N., Verdoux, H., et al. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. Psychological medicine, 32(2), 347–58. doi:10.1017/S0033291701005141

Sugranyes, G., Kyriakopoulos, M., Corrigall, R., Taylor, E., & Frangou, S. (2011). Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. PloS one, 6(10), e25322. doi:10.1371/journal.pone.0025322

Tomlin, D., Kayali, M. A., King-Casas, B., Anen, C., Camerer, C. F., Quartz, S. R., & Montague, P. R. (2006). Agent-specific responses in the cingulate cortex during economic exchanges. Science (New York, N.Y.), 312(5776), 1047–50. doi:10.1126/science.1125596

Van der Cruyssen, L., Van Duynslaeger, M., Cortoos, A., & Van Overwalle, F. (2009). ERP time course and brain areas of spontaneous and intentional goal inferences. Social neuroscience, 4(2), 165–84. doi:10.1080/17470910802253836

Van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychological medicine, 39(2), 179–95. doi:10.1017/S0033291708003814

Van Overwalle, F. (2009). Social cognition and the brain: a meta-analysis. Human brain mapping, 30(3), 829–58. doi:10.1002/hbm.20547

Van Overwalle, F., & Baetens, K. (2009). Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. NeuroImage, 48(3), 564–84. doi:10.1016/j.neuroimage.2009.06.009

Vollema, M.G., Sitskoorn, M.M., Appels, M.C.M., & Kahn, R.S. (2002). Does the Schizotypal Personality Questionnaire reflect the biological-genetic vulnerability to schizophrenia? Schizophrenia research, 54(1-2), 39–45. doi: 10.1016/S0920-9964(01)00350-4

Walter, H., Ciaramidaro, A., Adenzato, M., Vasic, N., Ardito, R.B., Erk, S., & Bara, B.G. (2009). Dysfunction of the social brain in schizophrenia is modulated by intention type: an fMRI study. Social cognitive and affective neuroscience, 4(2), 166–76. doi:10.1093/scan/nsn047

Wheaton, K.J., Pipingas, A., Silberstein, R.B., & Puce, A. (2001). Human neural responses elicited to observing the actions of others. Visual neuroscience, 18(3), 401–6. doi:10.1017/S0952523801183069

Wible, C.G., Preus, A.P., & Hashimoto, R. (2009). A Cognitive Neuroscience View of Schizophrenic Symptoms: Abnormal Activation of a System for Social Perception and Communication. Brain imaging and behavior, 3(1), 85–110. doi:10.1007/s11682-008-9052-1

Wible, C.G. (2012). Schizophrenia as a disorder of social communication. Schizophrenia research and treatment, 2012, 920485. doi:10.1155/2012/920485

Wischniewski, J., Windmann, S., Juckel, G., & Brüne, M. (2009). Rules of social exchange: game theory, individual differences and psychopathology. Neuroscience and biobehavioral reviews, 33(3), 305–13. doi:10.1016/j.neubiorev.2008.09.008

Wittchen, H.U., Wunderlich, U., Gruschwitz, S., Zaudig, M. (1997). Strukturiertes Klinisches Interview für DSM-IV (SKID). Göttingen, Hogrefe: Interviewheft und Beurteilungsheft.

Woods, S.W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. The Journal of clinical psychiatry, 64(6), 663–7. doi:10.4088/JCP.v64n0607

Supplement material

Table 1: *Brain areas showing increased activity to different conditions*

Area	MNI coordinates x	y	z	Cluster size	z value	Voxel level p FDR corr. (peak voxel)
$C+_{CONTR} > C-_{CONTR}$						
Right Superior Temporal Gyrus	69	-40	13	216	4.7	0.021
Right Middle Temporal Gyrus	51	-34	1		4.17	0.031
Right Superior Temporal Gyrus	48	-43	13		3.9	0.035
Left Precuneus	-3	-46	46	73	4.39	0.025
Right Middle Temporal Gyrus	51	-70	4	41	3.96	0.035
Right Superior Occipital Gyrus	18	-88	34	24	3.67	0.047
Left Middle Temporal Gyrus	21	-91	22		3.66	0.047
Left Inferior Parietal Lobule	-54	-67	16	21	3.63	0.047
	-48	-70	22		3.57	0.047
Right Superior Medial Gyrus	-51	-58	46	13	3.43	0.047
Left Supramarginal Gyrus	12	50	37	13	4.08	0.031
Left Inferior Frontal Gyrus (BA44)	-57	-52	31	8	3.51	0.047
	-60	17	16	7	4.02	0.032
$C-_{CONTR} > C+_{CONTR}$ n. s.						
$C+_{SCHIZ} > C-_{SCHIZ}$ n. s.						
$C-_{SCHIZ} > C+_{SCHIZ}$						
Left Middle Frontal Gyrus *	-33	23	37	7879	4.83	0.009
Left Middle Cingulate Cortex *	-6	-16	43		4.25	0.026
Left Superior Frontal Gyrus *	-12	44	31		4.25	0.026
Left Angular Gyrus *	-39	-55	28		4.25	0.026
Right Superior Temporal Gyrus	66	-22	-2	166	3.42	0.026
Right Middle Temporal Gyrus	63	-22	-11		3.14	0.030
Right Superior Temporal Gyrus	66	-10	-2		3.08	0.031
Left Middle Temporal Gyrus	-60	-25	1	75	3.10	0.030
Left Middle Temporal Gyrus	-63	-19	-11		2.78	0.036
Left Superior Temporal Gyrus	-60	-16	7		2.64	0.040
Left Paracentral Lobule	-6	-34	67	7	2.66	0.039
Right Superior Frontal Gyrus *	18	50	-2	6	2.74	0.037
$C-_{SCHIZ} > C-_{CONTR}$						
Right Precentral Gyrus (BA 6)	42	-10	52	854	4.29	0.038
Right Middle Cingulate Cortex	6	-28	46		4.10	0.038
Left Middle Cingulate Cortex *	-9	-25	43		3.94	0.038
Right Superior Frontal Gyrus *	24	29	49	643	4.08	0.038
Left Superior Frontal Gyrus *	-12	38	43		3.87	0.038
Right Superior Medial Gyrus	12	44	37		3.82	0.038
Right Putamen	27	2	13	154	4.02	0.038
	30	8	-5		3.65	0.038
Right Pallidum	24	2	-5		3.24	0.043
Left Postcentral Gyrus (BA 6)	-45	-13	49	140	4.59	0.038
Left Precentral Gyrus (BA 6)	-27	-13	55		2.88	0.049
Left Putamen	-24	-1	7	76	3.46	0.040
Right Angular Gyrus	45	-55	28	68	3.38	0.042
Right Superior Temporal Gyrus	60	-55	22		3.08	0.044
Right Inferior Parietal Lobule	60	-52	43		2.92	0.047
Right Anterior Cingulate Cortex	6	26	13	64	3.52	0.039
	9	38	4		3.23	0.043
Right Posterior Cingulate Cortex	9	-46	28	30	3.25	0.043
Left Anterior Cingulate Cortex	-9	38	7	18	3.14	0.044
$C+_{CONTR} > C+_{SCHIZ}$ n. s.						

*Separate t-tests. p<.05 FDR corr. k=5. * area significant in interaction analysis; Patients with schizophrenia (SCHIZ); control subjects (CONTR); nSCHIZ/nCONTR =19/19*

Table 2: *Brain areas showing increased activity compared to baseline in CONTR*

Area	MNI coordinates x	y	z	Cluster size	z value	Voxel level p FDR corr. (peak voxel)
$C-_{CONTR} > ISI_{CONTR}$						
Left Inferior Parietal Lobule (BA 40)	-33	-40	49	5562	7.27	0.000
Right Inferior Parietal Lobule (BA 40)	36	-34	49		7.14	0.000
Right Superior Parietal Lobule (BA 7)	36	-46	61		6.49	0.000
Left Precentral Gyrus (BA 6)	-27	-10	58	615	5.75	0.000
	-54	5	34		5.68	0.000
Right Superior Frontal Gyrus (BA 6)	30	-10	61	222	5.66	0.000
Right Inferior Frontal Gyrus (BA 44)	36	8	31	156	3.43	0.004
	54	11	31			
Right Cingulate Gyrus (BA 31)	21	-37	16	88	3.31	0.006
Left Posterior Cingulate (BA 29)	0	-40	7	77	3.24	0.007
Left Cerebellum	0	-34	-5		3.05	0.012
Left Caudate	-18	29	-2	65	3.47	0.004
Left Anterior Cingulate Gyrus (BA 32)	-15	23	13		2.94	0.016
Right Caudate	18	29	-5	52	3.86	0.001
Left Cingulate Gyrus (BA 31)	-21	-22	28	21	2.82	0.022
	-21	-31	22		2.60	0.038
$C+_{CONTR} > ISI_{CONTR}$						
Left Inferior Parietal Lobule (BA 40)	-33	-40	49	8169	7.65	0.000
Right Inferior Parietal Lobule (BA 40)	36	-34	49		7.45	0.000
Left Middle Occipital Gyrus (BA 19)	-24	-76	31		6.96	0.000
Right Superior Parietal Lobule (BA 7)	24	-58	58		6.27	0.000
Right Inferior Frontal Gyrus (BA 44)	42	8	34	372	4.09	0.000
Right Precentral Gyrus (BA 6)	27	-13	58	310	6.21	0.000
Left Posterior Cingulate Cortex (BA 29)	-3	-40	10	261	3.70	0.001
Right Cerebellum	3	-34	-2		3.23	0.005
Right Parahippocampal Gyrus (BA 30)	21	-34	16		2.91	0.013
Left Caudate Nucleus	-3	17	1	86	3.49	0.003
	-15	26	1		3.12	0.007
Right Caudate	18	29	-5	69	3.87	0.001
Right Middle Frontal Gyrus (BA 10)	30	62	7	34	3.02	0.010
Right Superior Temporal Gyrus (BA 40/42)	69	-34	19	26	3.11	0.008
Left Cingulate Gyrus (BA 31)	-21	-22	28	19	2.87	0.015
Left Thalamus	0	-16	13	12	2.53	0.034

t-tests, p<.05 FDR corr. k=10. Control subjects (CONTR); nCONTR =19;
ISI = inter-stimulus-interval i.e., baseline condition (scrambled picture of a video frame)

Impaired action information processing within the mirror neuron network in patients with schizophrenia*

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Abstract

Introduction: In schizophrenia, social cognition deficits are explained by alterations of the observation-execution matching system i.e., the mirror neuron system (MNS). This system is activated when subjects view or perform grasping movements. This simple task can be used to probe the integrity of the MNS. Surprisingly, just a few studies focus on the functionality of this system in schizophrenia.

Method: We carried out a functional magnetic resonance imaging study, measuring 19 patients with paranoid schizophrenia and 19 healthy matched controls while they observed and executed grasp-movements. Functional connectivity of the inferior frontal gyrus (IFG) and inferior parietal lobe (IPL), as part of the MNS, was compared between groups.

Results: Shared activation in response to observation and execution of grasp-movements was found in the typical MNS in schizophrenia and healthy controls. Significant differences in activation between both groups were observed in the right lingual gyrus (LNG). An analysis of functional connectivity revealed significantly decreased connectivity between parts of the MNS (i.e., bilateral IPL with right posterior sulcus temporalis superior and IFG; right IFG with right posterior sulcus temporalis superior and left precentral gyrus) as well as between the LNG and MNS regions in patients with schizophrenia compared to healthy controls.

Conclusions: Our findings suggest that a broader MNS dysconnectivity may be responsible for the social deficit in schizophrenia rather than specific primary focal brain abnormalities. We suggest that this altered connectivity reduces social functioning because it might disturb an essential sensory feedback exchange within the MNS.

Keywords: Mirror Neuron System I fMRI I Schizophrenia I Functional Connectivity I Lingual Gyrus

Introduction

Schizophrenia has been conceptualized as a disorder of the "social brain" (Burns, 2006). Social cognition deficits are counted among its core characteristics (Frith, 1992). Several domains of social cognition are affected: theory of mind abilities (ToM) (e.g., Bora et al., 2009; Brüne, 2005; Sprong, Schothorst, Vos, Hox, & Van Engeland, 2007), perception of cooperation (e.g., Backasch et al., in press), attributional biases (Langdon, Ward, & Coltheart, 2010), emotion recognition, social perception (Green et al., 2012) and imitation (Matthews, Gold, Sekuler, & Park, 2011; Park, Matthews, & Gibson, 2008). Action observation and understanding are prerequisites for various social cognition abilities (e.g., empathy, theory of mind, imitation). These abilities seem to have in common that they are subserved (amongst others) by the mirror neuron system (MNS; Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Rizzolatti, Fogassi, & Gallese, 2001, Rizzolatti & Fabbri-Destro, 2008). This network consists of neurons that discharge both during action production and observation of a similar action performed by another actor (in monkeys: Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996; in humans: Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010) - especially when hand-object-interactions are involved (Gallese et al., 1996; Iacoboni et al., 2005). The network provides a motor-based understanding of an observed motor act's goal performed by another individual through a mechanism that matches the motor act with an act in the observer's repertoire with the same goal (Rizzolatti & Sinigaglia, 2010).

The areas with mirror properties are functionally linked in a neural circuit. It is supposed that this MNS circuit in the human brain starts with coding early visual descriptions of observed actions in the superior temporal sulcus (STS). Subsequently, the information is sent to the inferior parietal lobe (IPL), which in turn transmits information signals to the premotor cortex including the inferior frontal gyrus (IFG, BA 44) (for reviews see Carr et al., 2003; Fabbri-Destro & Rizzolatti, 2008; Iacoboni & Dapretto, 2006; Rizzolatti et al., 2001; Rizzolatti & Craighero, 2004; Van Overwalle & Beatens, 2009). Then, information is passed back to the IPL (Iacoboni, 2005; Keysers & Perrett, 2004; Schippers & Keysers, 2011) and the STS (Iacoboni, 2009; for a discussion see Kilner, Friston, & Frith, 2007). Besides well-documented anatomical connections between STS and IPL as well as IPL and IFG in monkeys (Rizzolatti et al., 2001), evidence for connections has also been accumulated for humans (Frey, Campbell, Pike, & Petrides, 2008; Molinari et al., 2012; Tomassini et al., 2007).

In autism, a disorder associated with profoundly impaired social functioning, it has already been proposed that a dysfunction of the MNS could be responsible for social deficits (Dapretto et al., 2006; Perkins, Stokes, McGillivray, & Bittar, 2010; Rizzolatti & Fabbri-Destro, 2010), although the relationship is still controversial (e.g., Fan, Decety, Yang, Liu, & Cheng, 2010). Due to the phenomenological overlap between autism and schizophrenia in impaired social cognition e.g., ToM ability (see review in King & Lord, 2011) it has been assumed that patients with schizophrenia exhibit functional deficits in the MNS as well (Arbib & Mundhenk, 2005; Bertrand et al., 2008; Iacoboni & Dapretto, 2006).

Surprisingly, however, there is a lack of studies investigating MNS functioning in schizophrenia (Brunet-Gouet et al., 2011). A few studies showed an altered network for emotional observation that consists of MNS areas (e.g., Fahim et al., 2004; Park et al., 2009; Quintana, Davidson, Kovalik, Marder, & Mazziotta, 2001) but they did not include an execution condition in their experimental paradigms. To our knowledge, direct evidence for an altered activity of brain areas for shared representation of action execution and observation in schizophrenia comes to date only from three heterogeneous electrophysiological studies (Enticott et al., 2008; McCormick et al., 2012; Schürmann et al., 2007). Given the strong hypothesizing regarding a difference of MNS activity in schizophrenia on the one hand and scant empirical evidence for this notion on the other hand, we believe that social cognition deficits not caused by focal brain abnormalities within the MNS and there is a need to study interactions between MNS areas in schizophrenia using fMRI functional correlation analysis. The idea that schizophrenia in general is not a failure of focal brain functioning, but of pathological connectivity has been postulated several times (see Stephan, Friston, & Frith, 2009). However, in the context of MNS functioning this approach has not been studied in detail in schizophrenia, but in autism. Here, altered connectivity has been shown between IFG and other cortical areas (Shih et al., 2010; Villalobos, Mizuno, Dahl, Kemmotsu, & Müller, 2005).

In line with the reasoning of Enticott et al. (2008), we hypothesize that a neural functional dysconnectivity between areas of the MNS network in schizophrenia is responsible for action-perception matching and thus deficits in social cognition. In order to test this hypothesis we designed a MNS-task with hand-object interaction and three conditions: action observation, action execution and imitation. Besides fMRI brain activation analysis we evaluated functional connectivity to identify the extent to which activation levels in selected seed voxels of the MNS (BA 44 and IPL) are correlated with activation levels in the whole brain, and in parts of the MNS in particular. This correlation reflects the degree to which the regions are functionally connected (e.g., Friston, 1994). We expected that the functional connections between IFG and IPL as well as other MNS nodes are reduced in schizophrenia.

Material and Methods

2.1. Participants

Nineteen right-handed patients with paranoid schizophrenia (SCHIZ, without comorbid psychiatric disorders) diagnosed by two independent psychiatrists on the basis of interviews with patients and relatives as well as past and present chart notes, according to DSM-IV criteria (American Psychiatric Association, 1994) were included in the study. All patients were taking medication at the time of the study. Five patients were receiving typical neuroleptics and 14 atypical neuroleptics (see Tab.1, chlorpromazine equivalent dose; Woods, 2003). Additionally, four patients were receiving SSRI medication. All patients were being treated as inpatients or were attending the day-clinic of the local departments of psychiatry and psychotherapy.

A total of 19 right-handed healthy controls (CONTR) without a history of psychiatric disorders or first-degree relatives with psychotic illnesses took part in the study. To ensure the absence of psychiatric disorders the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) was conducted. Healthy controls were matched to the patient group on the basis of sex, age, education and intelligence (estimated using a German vocabulary test, the Mehrfachwahl-Wortschatz-Intelligenztest, MWT-B by Lehrl, Triebig, & Fischer, 1995). All subjects gave written informed consent and the local ethics committee approved the study protocol.

2.2. Experimental design and stimuli presentation

We used a MNS-task with object interaction and three conditions: action observation, action execution and imitation. While lying in the MRI scanner, participants had a 3x3 squared "mini-chessboard" on their lab, a chessman in their right hand and watched videos with an actor moving a chessman in a certain direction and back to the middle field (observation, O). This condition alternated with two separate conditions both without visual feedback: participants were either instructed to move their own chessman in exactly the same way as the actor seen before (action imitation, Ai) or to move the chessman in another way (action execution, Ae) (Figure 1). This procedure allows for an analysis of shared activation in the brain in response to all conditions and therefore, it is possible to evaluate brain areas with mirror properties, i. e., coding observation as well as action performance in the same neural structures. In detail, the observation (O) as well as the action conditions (Ae/Ai) lasted 4 s and the sequence of conditions was predefined in a pseudorandom order to avoid time-locked conditions. That means, that the observation tasks were not followed by the action conditions in general, rather they were presented in smaller blocks (e.g., O, O, O, Ae, Ai, Ae, O, Ai, Ae, O, O). The specific action task was indicated through a red fixation cross and either in combination with a target circle pointing on a certain field (Ae) or without a circle implying that partici-

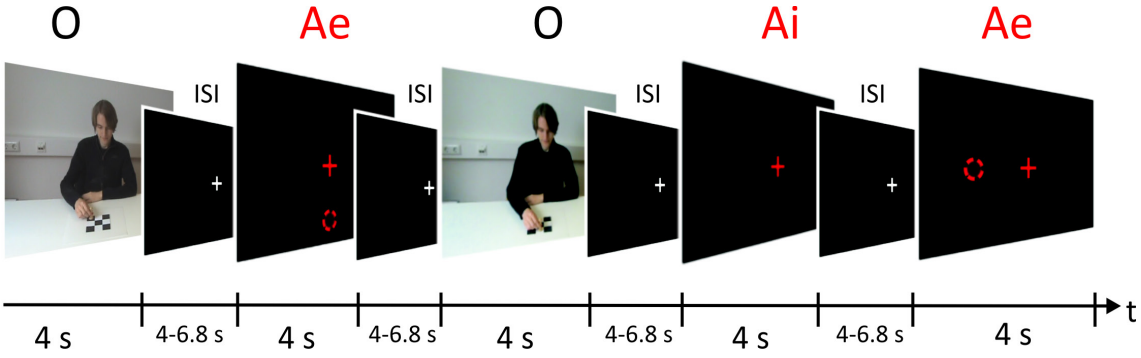

Figure 1: **Schematic representation of the stimuli:** *Participants watched videos showing an actor who is moving a chessman (O), followed by an inter stimulus interval of 4-6.8 s (ISI) and either a display of a fixation cross and a circle indicating how the participants should move the chessman by themselves (Ae) or a display without a circle indicating that they should imitate the action observed before (Ai).*

pants had to imitate the action observed in the last observation condition (Ai). The latter task was interspersed to ensure that the participants were attentively watching the videos (O). An inter-stimulus interval (ISI) with variable length (4-6.8 s) was introduced between conditions as a baseline condition to jitter stimulus onsets. After a training procedure outside the scanner in order to ensure that all participants are able to perform the task, participants underwent functional magnetic resonance imaging (fMRI) with the chessboard on their lap. Neither the chessboard nor the own actions were visible for the participants; the edges of the chessboard and an elevation of the middle field served as orientation. A total of 60 trials were performed (20 O-trials, 20 Ai-trials and 20 Ae-trials) while the BOLD (blood oxygen level dependent) response was measured. The hand movements were videotaped and the task performance was controlled on-line by the experimenter.

2.3. FMRI data acquisition

Participants were scanned at 3T scanner (Siemens Trio, Erlangen, Germany) with 36 near-axial slices and a distance factor of 10% providing whole brain coverage. An echo planar imaging (EPI) sequence was used for acquisition of 354 functional volumes during the experiment (repetition time = 2.19 s, echo time = 30 ms, flip angle = 90°, slice thickness = 3 mm, field of view = 192 mm, voxel resolution = 3 x 3 mm). After the functional run, an anatomical high-resolution T1-weighted 3-D scan was acquired (repetition time = 1.9 s, echo time = 2.52 ms, flip angle = 9°, slice thickness = 1 mm, field of view = 256 mm, voxel resolution = 1 x 1 mm, inter-slice gap = 0.5 mm). The whole paradigm lasted for 12.9 min.

2.4. FMRI data analysis

Functional MRI data were analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.5 (Mathworks Inc., Sherborn, Mass., USA). The first 11 volumes of the session (dummy images), which were acquired while participants read the final instructions, were discarded from further analyses. At first the remaining scans and the structural image were manually assigned to the anterior commissure. To correct for head movement artifacts the functional images were realigned for each subject to the first image of each time series and again realigned to the mean image. All functional images were corrected for a temporal shift in acquisition (slice timing). Afterwards, the resulting mean functional image was co-registered with the high-resolution structural T1 image to align the latter in the same space as the functional images. Subsequently, individual T1 images were segmented based on gray and white matter and the revealed parameters were used for spatial normalization for the functional images to the standard stereotactic space defined by the Montreal Neurological Institute (MNI) template and resliced with a voxel size of 3×3×3 mm. Finally, they were spatially smoothed using a 10 mm full width at half maximum (FWHM) isotropic Gaussian kernel to accommodate intersubject variation in brain anatomy, and high-pass filtered at 1/128 Hz to remove low frequency drifts.

Table 1: *Demographic and clinical characteristics of study participants*

	SCHIZ (n=19)	CONTR (n=19)	Statistics
Mean age (years)	30.0 ± 8.0	32.6 ± 8.7	n.s.
Male to female ratio	18:1	18:1	
Intelligence	107.1 ± 15.6	110.7 ± 16.1	n.s.
Mean duration of Illness (years)	8.0 ± 6.8	-	-
SANS	23.1 ± 19.3	-	-
SAPS	18.9 ± 11.2	-	-
Mean CPZ equivalents (mg)	745.6 ± 500.8	-	-

Patients with schizophrenia (SCHIZ); control subjects (CONTR); ± indicates the standard deviation; Scale for the Assessment of Negative Symptoms (SANS); Scale for the Assessment of Positive Symptoms (SAPS); chlorpromazine equivalent dose (CPZ), n.s. indicates non-significant differences in a t-test comparison

Task Activation Analysis

To look for areas of overlap of activation in execution and observation conditions and thus reveal the MNS we used a test for conjunction ("conjunction null" implemented in SPM8, as proposed by Nichols, Brett, Andersson, Wager, & Poline, 2005). Therefore the regressors of interest (O,Ai,Ae) were modeled with a duration of 4 s and compared separately to baseline activation (ISI) for each participant. At first, the conjunction was build in both groups separately [O∩(Ai+Ae)]. For comparisons of overlapping activations in patients and healthy controls and thereby testing the hypothesis of altered MNS in schizophrenia, we computed difference contrasts for the conditions separately: We compared activation in controls versus patients both in response to observation ($O_{CONTR}>O_{SCHIZ}$) and the two action conditions combined ($Ai+Ae_{CONTR}>Ai+Ae_{SCHIZ}$). Afterwards, we performed a conjunction analysis with these contrasts [($O_{CONTR}>O_{SCHIZ}$)∩($A_{CONTR}>A_{SCHIZ}$)] resulting in regions that are differently recruited during observation and action performance in patients compared to controls (see supplementary Fig.1 for additional details). The locations of the activation maxima were reported as MNI-coordinates (Brett, Johnsrude, & Owen, 2002) and family-wise error-corrected (FWE p<.05 at peak level, corrected for whole brain analysis).

Functional Connectivity Analysis

In addition to examining differences in levels of brain activity for conditions and groups, we also studied functional connectivity MRI (fcMRI) using the seed-voxel approach. With regard to our prespecified hypotheses, i.e., an altered connectivity between MNS areas rather than specific dysfunction of activation within MNS areas in schizophrenia, we identified the extent to which activation levels in selected seed voxels within the MNS are correlated, i.e. functionally connected. First, we defined four seed regions that are known to be key regions of the action observation–execution-matching system. On the basis of results from a conjunction analysis [O∩(Ai+Ae)] in all participants, we chose the group peak voxel activity of the bilateral inferior frontal gyrus (IFG, pars opercularis) at MNI-coordinates [-51,5, 28; 54, 10, 28] and the bilateral inferior parietal lobe (IPL) at [-36,-43,46; 36,-43,52]. Starting at these peak activations on the group level, we identified the next local maximum within each subject (in clusters exceeding 5 voxels) to account for interindividual alterations in activation patterns for the observation condition versus baseline (O>ISI, p<0.1 uncorrected). We limited this procedure by using a restriction to IFG and IPL masks (using Wake Forest Pick Atlas toolbox for SPM 8 (http://fmri.wfubmc.edu)). Second, we extracted individual time series from all seed regions in a sphere of a 5 mm radius. We corrected the extracted time series for task-related variance and noise by setting an effects-of-interest F-contrast on the six movement parameters. Third, we built a new first level design matrix to describe brain connectivity of the seed region with the whole, individual brain. Therein, we included the seed-time series, task, noise and movement regressors and set the T-contrast on the time series to generate individual connectivity maps. Correlations between seed time series and each voxel in the brain were examined according to Bedenbender et al. (2011).

Fourth, we performed a second-level group analysis. The connectivity maps were compared across groups using four two-sample t-tests for seeds individually (see supplementary Fig.2). We performed ROI-analyses within regions known to be activated in action observation as well as execution according to a recent meta-analysis by Molenberghs, Cunnington, and Mattingley (2012). The ROI mask consisted of bilateral IFG (BA 44), IPL, BA 6 and pSTS (sphere of 10 mm around [±51,-43, 22]). The locations of altered connectivity were reported on the level of p<.05 FWE corrected on peak level.

Results

At first, the on-line monitoring by the experimenter revealed that all subjects carried out the task correctly. At the beginning of this section we describe the results of the task activation analysis and report similarities in the observation-execution matching system as well as differences in levels of brain activity obtained in

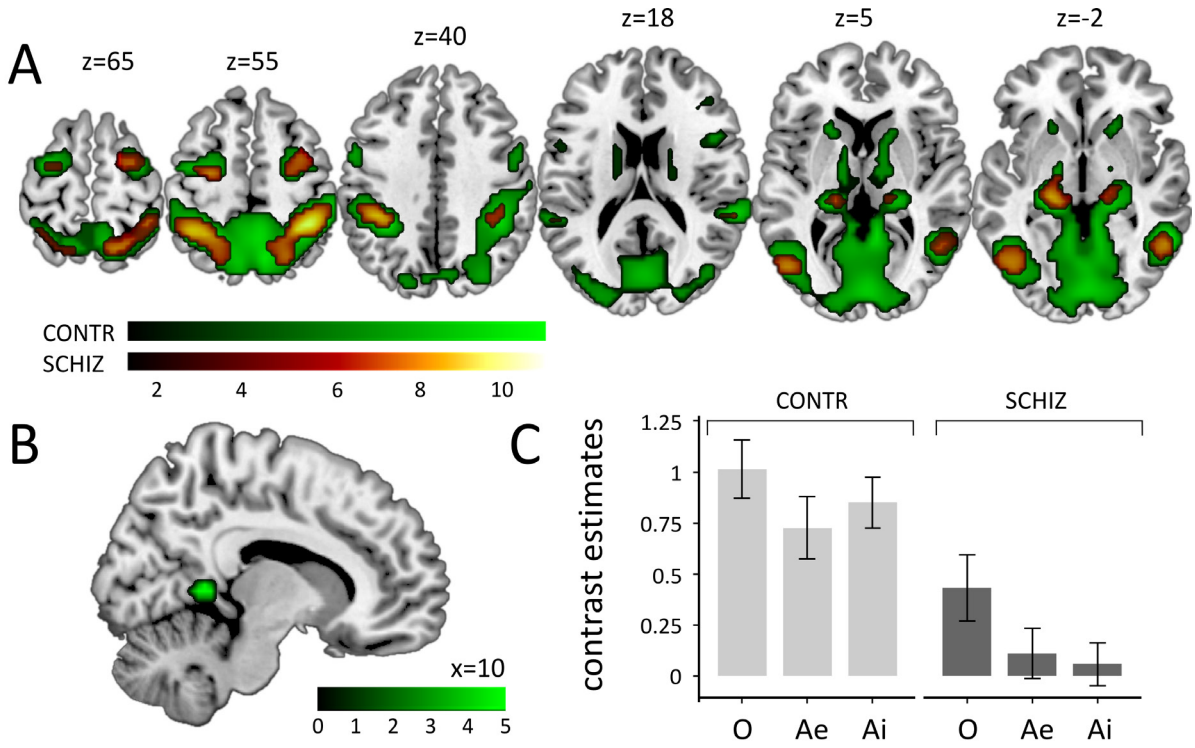

Figure 2.: Areas involved in observation-execution matching in SCHIZ and CONTR. *(**A**) Conjunction analysis [O∩(Ai+Ae)] for both groups separately revealed overlapping regions in healthy controls (CONTR, in green) and patients with schizophrenia (SCHIZ, in orange); n_{SCHIZ}=19, n_{CONTR}=19; for illustration purposes we chose a threshold of T>6; color bars show the corresponding T-value. (**B**) Significant differences within the observation-execution matching network between groups were found in the right lingual gyrus (significant at peak level, FWE = p<.05); [(O_{CONTR}>O_{SCHIZ})∩(Ai+Ae_{CONTR}>Ai+Ae_{SCHIZ})] (**C**) shows mean contrast estimates extracted from the lingual gyrus cluster at [9,-49,7]. Error bars indicate the standard error of the mean.*

patients with schizophrenia (SCHIZ) and healthy controls (CONTR). Afterwards, we refer to differences in functional connectivity within this network between groups.

Areas involved in observation-execution matching in both groups

Conjunction analysis of activity in the observation (O), action execution (Ae) and imitation (Ai) condition revealed a widespread network encompassing regions that are activated during both action observation and execution. Main activation centers, for both patients and controls, were found in the bilateral inferior parietal lobe (IPL), right superior parietal lobe (SPL), bilateral BA 6 (including precentral gyrus and supplementary motor area), bilateral inferior frontal gyrus (IFG, BA 44), and temporal areas (such as the right posterior sulcus temporalis superior (pSTS), middle temporal gyrus, and bilateral fusiform gyrus) (Fig.2 and supplementary Tab.1). The overlap of main activation clusters showed that patients and controls recruit a very similar network, even though with smaller cluster sizes in patients (see Fig.2). Although, we included the Ai condition primarily to maintain the participant's attention to the videos, we compared brain activation in response to Ai with Ae. Irrespective of direction, this analysis revealed no significant differences between conditions (p>.05 FWE corr.). As a consequence, we combined both to one action condition (Ae+Ai) in the performed analysis.

Differences in levels of brain activity in the observation-execution matching system in SCHIZ

Importantly, significant differences between brain activity in CONTR and SCHIZ were found using a conjunction analysis [(O_{CONTR}>O_{SCHIZ}) ∩ (Ai+Ae_{CONTR}>Ai+Ae_{SCHIZ})] in the right lingual gyrus (LNG) extending to parahippocampal regions at

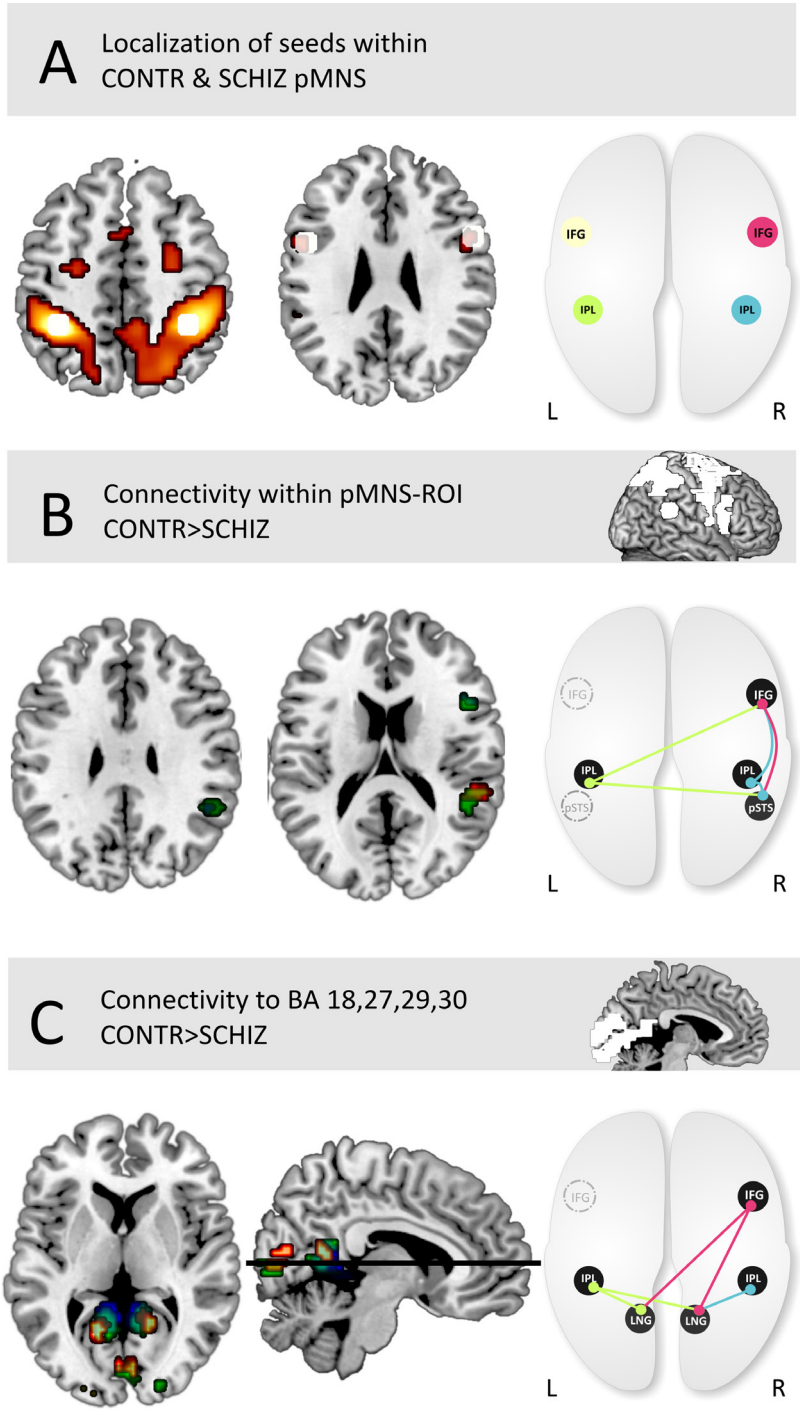

Figure 3.: Reduced connectivity in SCHIZ, compared to CONTR in the execution-observation matching network: A *shows seeds in IFG and IPL indicated through white blobs centered on peak activity at [-51,5, 28; 54, 10, 28] and [-36,-43,46; 36,-43,52]. Reduced functional connectivity of seeds (IPL in blue (R) and green (L), right IFG in red) to (**B**) other MNS regions and (**C**) regions centered on the LNG in schizophrenia. P's<.05, peak level, FWE corr.*

[9,-49,7] (cluster size 15 voxels, p=.006 significant at peak level, FWE corr., z=4.82) (Fig.2B). The contrast estimates for the differently activated cluster indicated significantly less activation in SCHIZ than in CONTR for all three conditions (Fig.2C; all p's<.05 using t-tests).

Table 2. *Seeds and areas in MNS-ROI with reduced functional connectivity in SCHIZ*

Seeds & associated Areas	***L/R***	***MNI coordinates***			***Cluster size***	***z value***	***peak level p FWE corr.***
		x	y	z			
IPL left							
Sulcus temporalis superior	R	51	-46	25	60	4.95	0.001
Inferior frontal gyrus	R	48	17	16	17	4.58	0.004
IPL right							
Sulcus temporalis superior	R	51	-46	28	3	3.96	0.042
Inferior frontal gyrus	R	51	17	16	5	4.13	0.016
IFG right							
Sulcus temporalis superior	R	54	-37	16	21	4.48	0.006
Precentral gyrus (BA 6)	L	-45	-4	43	6	4.09	0.027

Seeds highlighted in green, CONTR>SCHIZ, nSCHIZ=19, nCONTR=19, L/R indicates the hemisphere (left/right), p<.05 FWE corr.

Differences in functional connectivity

To investigate differences of functional connectivity in the execution-observation network between groups, we chose seeds from the best-validated nodes of the MNS, namely the IPL and IFG. The connectivity maps of all seeds revealed a widespread network (see supplementary Fig.3). Therefore we limited further statistical analysis between groups to ROIs within MNS regions (see Fig.3B, upper right).

Both IPL seed time series showed significantly lower correlations with the right pSTS and right IFG in patients with schizophrenia (see Tab.2, Fig.3B) than in controls. Significantly reduced functional connectivity in SCHIZ were also found between the right IFG and a cluster within the right pSTS and left BA 6 (Tab.2, Fig.3B). No significant differences were found for the left IFG within the selected ROIs (for whole brain comparison see supplementary Fig.4). With respect to the finding of altered LNG recruitment in patients, we investigated the functional connectivity between MNS seeds and a ROI including the LNG as well as adjacent Brodmann areas (Fig.2B). We found reduced connectivity between all seeds (except left IFG) and the bilateral LNG as well as adjacent occipital, temporal, and parietal areas in patients with schizophrenia compared to controls (for further details see supplementary Tab.2).

Discussion

To our knowledge, we present the first study using fMRI to explore the functionality of the mirror circuit in schizophrenia. The primary goal was to determine possible neural differences in this observation-execution system in patients with schizophrenia compared to a healthy control group. Three main results were obtained: (1) the observation-execution matching system comprises similar MNS associated areas in healthy controls (CONTR) and patients with schizophrenia (SCHIZ). (2) Besides smaller activated clusters in patients, we found significant differences in the recruitment of the lingual gyrus. (3) We could show that regions within the network for observation-execution matching (e.g., right IFG, bilateral IPL, right pSTS, and the bilateral lingual gyrus) are less connected in SCHIZ compared to CONTR. In the following the results are discussed in this order.

Areas involved in observation-execution matching

As assumed, we found no significant differences in activity of the MNS in response to observation and execution of grasping actions in patients with schizophrenia compared to healthy controls. In line with our hypothesis, the within group conjunction analysis (obser-

vation ∩ action) revealed for both groups regions previously linked to mirror properties (see meta-analysis by Molenberghs et al., 2012) such as premotor areas (including inferior frontal gyrus (IFG)), parietal areas (including inferior parietal lobe (IPL) and superior parietal lobe), temporal areas (including posterior sulcus temporalis superior (STS)). This indicates that the paradigm was suitable to test our hypothesis.

Differences in levels of brain activity in the observation-execution matching system in SCHIZ

Significant difference in activity in shared representation for observation and action performance in SCHIZ [(O_{CONTR}>O_{SCHIZ})∩(Ai+Ae-$_{CONTR}$>Ai+Ae_{SCHIZ})] was only found in the right ventromedial occipitotemporal cortex, more precisely the rostral part of the lingual gyrus (LNG) extending to posterior parahippocampal regions. This area was less activated in patients in all conditions. The contrast estimates indicate that in addition to being activated by action of others, it is also modulated by planning and executing movements at least in controls, whereas in patients it is less activated in execution conditions. Accordingly, this is frequently reported in studies dealing with imitation (e.g., Lee, Josephs, Dolan, & Critchley, 2006; Koski, Iacoboni, Dubeau, Woods, & Mazziotta, 2003), observation of movements (e.g., Astafiev, Stanley, Shulman, & Corbetta, 2004; Decety & Grèzes, 1999; Lotze et al., 2006; Molnar-Szakacs, Kaplan, Greenfield, & Iacoboni, 2006; Pelphrey, Morris, Michelich, Allison, & McCarthy, 2005; Weissman, Perkins, & Woldorff, 2008) - especially from the third person perspective (Hesse, Sparing, & Fink, 2009; Hétu, Mercier, Eugène, Michon, & Jackson, 2011; Jackson, Meltzoff, & Decety, 2006; Wurm, Von Cramon, & Schubotz, 2011), and execution (Filimon, Nelson, Hagler, & Sereno, 2007). Moreover the LNG seems to respond to both observation and execution of mouth movements (Pfeifer, Iacoboni, Mazziotta, & Dapretto, 2008; Van der Gaag, Minderaa, & Keysers, 2007; Wild, Erb, Eyb, Bartels, & Grodd, 2003) or finger lifting (Williams et al., 2006) and therefore also showed mirror properties in other studies. Actually, we do not know whether the LNG contains multimodal mirror neurons or not, but a recent electrophysiological study suggests that this is the case at least for the adjacent parahippocampus (Mukamel et al., 2010). Therefore, our finding does not necessarily reflect a specific mirror impairment. Instead, it is more likely that the LNG, which is both interconnected with the parahippocampus (Powell et al., 2004) and a part of the ventral pathway in visual information processing (Mishkin, Ungerleider, & Macko, 1983) that perceives and processes visuo-spatial information, could be involved in encoding visual information for subsequent memory recall or mental rotation (Schendan & Stern, 2008). In line with this, it was necessary in the present study, at least for correct imitation, to remember and mentally rotate the action of the actor that was seen from the third person perspective. These required processes might have been affected in patients, as shown by other studies investigating visual (e.g., Coleman, Krastoshevsky, Tu, Mendell, & Levy, 2012; Haenschel et al., 2007) and spatial working memory (e.g., Kang, Sponheim, Chafee, & MacDonald, 2011). Accordingly, Haenschel et al. (2007) demonstrated that deficits in early sensory and perceptual processing in occipital regions are associated with defective visual information encoding and visual working memory retrieval. Besides that, several structural alterations in the right LNG such as increased gyrification but reduced cortical thickness in the right parahippocampal–lingual cortex (Schultz et al., 2010) or reduced gray matter volume (e.g., Borgwardt et al., 2010; Mané et al., 2009) might be associated with these functional deficits in schizophrenia. Interestingly, patients with autism seem to have LNG-related deficits as well– like reduced gray matter volume (Ecker et al., 2012) and lower recruitment in response to an imitation task (Williams et al., 2006).

The question may arise why we failed to confirm findings for altered activation within the MNS in schizophrenia. First, although some authors

observed altered activation in areas associated with mirror neurons (e.g., Fahim et al., 2004; Kato et al., 2011; Park et al., 2009; Quintana et al., 2001), they did not include the essential execution condition in their study design and therefore could not test for mirror properties. Second, electrophysiological studies by Schürmann et al. (2007), Enticott et al. (2008), and McCormick et al. (2012) which considered this point, are difficult to compare with fMRI data and focused on specific areas only (i.e., premotor, motor or sensorimotor cortex). Third and most importantly, results were inconsistent between these studies. Besides that, they mostly used heterogeneous patient groups. We therefore studied a more homogeneous group consisting of patients with paranoid schizophrenia exclusively - with the vast majority showing psychotic symptoms - compared to well-matched controls. Based on the fact that evidence for a specific effect of an altered activation pattern within the MNS is rare, and the lack of findings in our study, we suggest that the social deficit in schizophrenia may underlie a broader MNS dysconnectivity.

Differences in functional connectivity in CONTR and SCHIZ

A "dysconnectivity model" of schizophrenia has already been proposed before and a number of cfMRI studies revealed altered connectivity in complex prefrontal and cerebellar-thalamic-prefrontal networks in schizophrenia (see Schmitt, Hasan, Gruber, & Falkai, 2011 for a summary). To date, no fcMRI study on schizophrenia has investigated the connectivity of brain areas focusing on the MNS. We found that in schizophrenia, the functional connectivity among the most frequently cited MNS areas, namely right IFG and bilateral IPL, and their input region, the right posterior STS, is significantly reduced. The resulting network nodes are in line with anatomical connections found in other studies. In the human brain the IPL and STS as well as IFG and IPL are linked via the superior longitudinal fasciculus (Catani, Jones, & ffytche, 2005; Duffau, 2008; Makris et al., 2005). Furthermore, Schippers and Keysers (2011) showed that the MNS network acts as a dynamic control system, in a way that besides the well established information flow from temporal to parietal and subsequently to premotor areas, the information predominantly flows in reverse direction. Our data suggest that irrespective of their direction, the flows within the MNS seem to be affected in patients with schizophrenia. Additionally, the alterations are more right lateralized concerning connections both to and within the right hemisphere, whereas the connectivity of the left IFG showed no significant modifications within the MNS. Lateralization effects in schizophrenia in terms of underactivity in right-hemisphere structures and overactivity in left-hemisphere structures have been found before in social cognitive tasks recruiting mirror areas (de Achával et al., 2012). One can assume that those effects could be the result of decreased right-hemisphere connectivity observed in our study and suggest that patients with schizophrenia might rely rather on unaffected left-hemisphere components (like the left IFG-IPL-STS connection) during social cognitive tasks.

Furthermore, due to the reduced connectivity between higher visual areas (most notably the LNG) and both the bilateral IPL and the right IFG, we suggest that the network is already impaired at the stage of visual processing. These facts highlight once again a similarity to findings in autism studies where decreased connectivity between IPL and IFG (Shih et al., 2010) and between early visual areas (BA 17) and IFG (Villalobos et al., 2005) can also be found. Interestingly, some evidence of functional coupling of visual (including LNG) and motor areas has recently been brought up by Pavlidou, Schnitzler, and Lange (2012). Among others, they suggest that the visual cortex might be influenced (by proprioceptive information in sensorimotor areas) via back-projections through association areas in the parietal lobe (Astafiev et al., 2004; Macaluso, Frith, & Driver, 2000) - probably aiming to update visual processing (Schippers & Keysers, 2011). In our paradigm, participants moved a chessman in the absence

of visual feedback. As a result they had to memorize actions seen before and mentally simulate the own action. To accomplish the appropriate movement, the parahippocampal-lingual cortex may receive input from IPL - either for activating memory encoding or action representation. This is in line with the suggestion of Schendan and Stern (2008) who mentioned that this area might be engaged in matching internal representations of observed scenes and a current percept. Comparably, it has been suggested that the STS, which we could show is also less synchronized with other parts of the MNS, receives an efference copy from the fronto-parietal MNS for matching motor plans with visual descriptions of the observed action (Iacoboni et al., 2001; Iacoboni & Dapretto, 2006; Leube et al., 2003; Molenberghs, Brander, Mattingley, & Cunnington, 2010). Indeed, there is plenty of evidence for an altered matching mechanism in schizophrenia (e.g., Lindner, Thier, Kircher, Haarmeier, & Leube, 2005; Maeda et al., 2012; Synofzik, Thier, Leube, Schlotterbeck, & Lindner, 2010), which results in having difficulty to distinguish between own actions and actions of others (i.e., disturbed sense of agency) reflecting a first rank symptom in schizophrenia (Frith, Blakemore, & Wolpert, 2000). Our findings point out that the essential sensory feedback exchange, either proprioceptive or motor plan information, could be affected in schizophrenia due to a poor MNS connectivity, which has been similarly mentioned before in autism (Williams et al., 2006).

Limitations

These novel findings should be interpreted carefully. The construct of the MNS in humans and the accessibility of its function using brain-imaging techniques have not remained unchallenged (e.g., Turella, Pierno, Tubaldi, & Castiello, 2009). Nevertheless, our findings of the MNS activation in healthy controls are in accordance with the recent literature. However, some factors like medication as well as differences in illness duration and number of psychotic episodes within the patient group could have influenced our results. In addition, besides the on-line monitoring by the experimenter, who ensured that participants place the chessman correctly, we had no assessment of task performance. However, mirror neuron processes are deemed to be relatively automatic (Iacoboni et al., 2005) and therefore watching and executing should be sufficient to elicit mirror neuron activation. It has to be mentioned that combining the two execution conditions (Ai+Ae) might have influenced the results, at its worst, mask potential differences in MNS activation. Previous research suggests that the MNS is sensitive to specific motor action, showing for example greater IPL and IFG activation while performing complementary grasp-movements compared to exact imitation (Newman-Norlund, van Schie, van Zuijlen, & Bekkering, 2007). However, the authors compared power with precision grip, whereas our execution conditions (Ae, Ai) are similar with respect to the performed grasp-movement, provided visual guidance and the absence of visible actions while executing. They differ only in the direction of the performed movement compared to the video observed before. Furthermore, the brain response to both conditions did not differ significantly and both conditions can therefore combined.

Conclusions

In this article, we provide the first fMRI evidence for an atypical connectivity focusing on the MNS network in schizophrenia. Given that the mirror neuron functionality is accepted as neurophysiological foundation of social cognitive abilities in humans (Gallese & Sinigaglia, 2011; Iacoboni & Dapretto, 2006), this newly observed right-lateralized MNS dysconnectivity might be a major contributor to social cognitive aberrances in schizophrenia - e.g., imitation (seen in our study), mentalizing (e.g., Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012), and empathizing deficits (e.g., Varcin, Bailey, & Hendry, 2010), as well as attributional style (e.g., Park et al., 2009). According to Fett et al. (2011), a reduction of these abil-

ities results in abnormal social functioning in schizophrenia. For a partial compensation one could assume that patients might rely rather on left-hemisphere components, which seem not to be affected, or on less-efficient, non-simulation neural networks. The observed altered activation and synchronization of the lingual gyrus with the MNS could reflect a disturbed exchange of sensory information for action representation in schizophrenia. Interestingly, our findings agree in many points with those found in autism, suggesting that they partly share MNS and visual processing deficits.

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References

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders. (4th ed.). Washington DC: American Psychiatric Association.

Arbib, M. A., & Mundhenk, T. N. (2005). Schizophrenia and the mirror system: an essay. Neuropsychologia, 43(2), 268–80. doi:10.1016/j.neuropsychologia.2004.11.013

Astafiev, S. V., Stanley, C. M., Shulman, G. L., & Corbetta, M. (2004). Extrastriate body area in human occipital cortex responds to the performance of motor actions. Nature neuroscience, 7(5), 542–8. doi:10.1038/nn1241

Backasch, B., Straube, B., Pyka, M., Klöhn-Saghatolislam, F., Müller, M.J., Kircher, T.T.J., & Leube, D.T. (in press). Hyperintentionality during automatic perception of naturalistic cooperative behavior in patients with schizophrenia. Social Neuroscience

Bedenbender, J., Paulus, F. M., Krach, S., Pyka, M., Sommer, J., Krug, A., Witt, S. H., et al. (2011). Functional connectivity analyses in imaging genetics: considerations on methods and data interpretation. (Y. He, Ed.) PloS one, 6(12), e26354. doi:10.1371/journal.pone.0026354

Bertrand, M.-C., Achim, A. M., Harvey, P.-O., Sutton, H., Malla, A. K., & Lepage, M. (2008). Structural neural correlates of impairments in social cognition in first episode psychosis. Social neuroscience, 3(1), 79–88. doi:10.1080/17470910701563491

Bora, E., Yucel, M., & Pantelis, C. (2009). Theory of mind impairment in schizophrenia: meta-analysis. Schizophrenia research, 109(1-3), 1–9. doi:10.1016/j.schres.2008.12.020

Borgwardt, S. J., Picchioni, M. M., Ettinger, U., Toulopoulou, T., Murray, R., & McGuire, P. K. (2010). Regional gray matter volume in monozygotic twins concordant and discordant for schizophrenia. Biological psychiatry, 67(10), 956–64. doi:10.1016/j.biopsych.2009.10.026

Brett, M., Johnsrude, I. S., & Owen, A. M. (2002). The problem of functional localization in the human brain. Nature reviews. Neuroscience, 3(3), 243–9. doi:10.1038/nrn756

Brunet-Gouet, E., Achim, A. M., Vistoli, D., Passerieux, C., Hardy-Baylé, M.-C., & Jackson, P. L. (2011). The study of social cognition with neuroimaging methods as a means to explore future directions of deficit evaluation in schizophrenia? Psychiatry research, 190(1), 23–31. doi:10.1016/j.psychres.2010.11.029

Brüne, M. (2005). "Theory of mind" in schizophrenia: a review of the literature. Schizophrenia bulletin, 31(1), 21–42. doi:10.1093/schbul/sbi002

Burns, J. (2006). The social brain hypothesis of schizophrenia. World psychiatry : official journal of the World Psychiatric Association (WPA), 5(2), 77–81.

Carr, L., Iacoboni, M., Dubeau, M.-C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proceedings of the National Academy of Sciences of the United States of America, 100(9), 5497–502. doi:10.1073/pnas.0935845100

Catani, M., Jones, D. K., & ffytche, D. H. (2005). Perisylvian language networks of the human brain. Annals of neurology, 57(1), 8–16. doi:10.1002/ana.20319

Coleman, M. J., Krastoshevsky, O., Tu, X., Mendell, N. R., & Levy, D. L. (2012). The effects of perceptual encoding on the magnitude of object working memory impairment in schizophrenia. Schizophrenia research, 139(1-3), 60–5. doi:10.1016/j.schres.2012.05.003

Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., & Iacoboni, M. (2006). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. Nature neuroscience, 9(1), 28–30. doi:10.1038/nn1611

Das, P., Lagopoulos, J., Coulston, C. M., Henderson, A. F., & Malhi, G. S. (2012). Mentalizing impairment in schizophrenia: a functional MRI study. Schizophrenia research, 134(2-3), 158–64. doi:10.1016/j.schres.2011.08.019

De Achával, D., Villarreal, M. F., Costanzo, E. Y., Douer, J., Castro, M. N., Mora, M. C., Nemeroff, C. B., et al. (2012). Decreased activity in right-hemisphere structures involved in social cognition in siblings discordant for schizophrenia. Schizophrenia research, 134(2-3), 171–9. doi:10.1016/j.schres.2011.11.010

Decety, J., & Grèzes, J. (1999). Neural mechanisms subserving the perception of human actions. Trends in Cognitive Sciences, 3(5), 172–178. doi:10.1016/S1364-6613(99)01312-1

Duffau, H. (2008). The anatomo-functional connectivity of language revisited. New insights provided by electrostimulation and tractography. Neuropsychologia, 46(4), 927–34. doi:10.1016/j.neuropsychologia.2007.10.025

Ecker, C., Suckling, J., Deoni, S. C., Lombardo, M. V, Bullmore, E. T., Baron-Cohen, S., Catani, M., et al. (2012). Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: a multicenter magnetic resonance imaging study. Archives of general psychiatry, 69(2), 195–209. doi:10.1001/archgenpsychiatry.2011.1251

Enticott, P. G., Hoy, K. E., Herring, S. E., Johnston, P. J., Daskalakis, Z. J., & Fitzgerald, P. B. (2008). Reduced motor facilitation during action observation in schizophrenia: a mirror neuron deficit? Schizophrenia research, 102(1-3), 116–21. doi:10.1016/j.schres.2008.04.001

Fabbri-Destro, M., & Rizzolatti, G. (2008). Mirror neurons and mirror systems in monkeys and humans. Physiology (Bethesda, Md.), 23(3), 171–9. doi:10.1152/physiol.00004.2008

Fahim, C., Stip, E., Mancini-Marïe, A., Boualem, M., Malaspina, D., & Beauregard, M. (2004). Negative socio-emotional resonance in schizophrenia: a functional magnetic resonance imaging hypothesis. Medical hypotheses, 63(3), 467–75. doi:10.1016/j.mehy.2004.01.035

Fan, Y.-T., Decety, J., Yang, C.-Y., Liu, J.-L., & Cheng, Y. (2010). Unbroken mirror neurons in autism spectrum disorders. Journal of child psychology and psychiatry, and allied disciplines, 51(9), 981–8. doi:10.1111/j.1469-7610.2010.02269.x

Fett, A.-K. J., Viechtbauer, W., Dominguez, M.-G., Penn, D. L., Van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. Neuroscience and biobehavioral reviews, 35(3), 573–88. doi:10.1016/j.neubiorev.2010.07.001

Filimon, F., Nelson, J. D., Hagler, D. J., & Sereno, M. I. (2007). Human cortical representations for reaching: mirror neurons for execution, observation, and imagery. NeuroImage, 37(4), 1315–28. doi:10.1016/j.neuroimage.2007.06.008

Frey, S., Campbell, J. S. W., Pike, G. B., & Petrides, M. (2008). Dissociating the human language pathways with high angular resolution diffusion fiber tractography. The Journal of neuroscience : the official journal of the Society for Neuroscience, 28(45), 11435–44. doi:10.1523/JNEUROSCI.2388-08.2008

Friston, K. J. (1994). Functional and effective connectivity in neuroimaging: A synthesis. Human Brain Mapping, 2(1-2), 56–78. doi:10.1002/hbm.460020107

Frith, C. D., Blakemore, S.-J., & Wolpert, D. M. (2000). Explaining the symptoms of schizophrenia: Abnormalities in the awareness of action. Brain Research Reviews, 31(2-3), 357–363.

Frith, C. D. (1992). The cognitive neuropsychology of schizophrenia. (N. Hillsdale, Ed.) (p. xiv 169 pp.). UK: Psychology Press.

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. Brain, 119(2), 593–609. doi:10.1093/brain/119.2.593

Gallese, V., & Sinigaglia, C. (2011). What is so special about embodied simulation? Trends in cognitive sciences, 15(11), 512–9.

doi:10.1016/j.tics.2011.09.003

Green, M. F., Bearden, C. E., Cannon, T. D., Fiske, A. P., Hellemann, G. S., Horan, W. P., Kee, K., et al. (2012). Social cognition in schizophrenia, Part 1: performance across phase of illness. Schizophrenia bulletin, 38(4), 854–64. doi:10.1093/schbul/sbq171

Haenschel, C., Bittner, R. A., Haertling, F., Rotarska-Jagiela, A., Maurer, K., Singer, W., & Linden, D. E. J. (2007). Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia: a study with event-related potentials and functional magnetic resonance imaging. Archives of general psychiatry, 64(11), 1229–40. doi:10.1001/archpsyc.64.11.1229

Hesse, M. D., Sparing, R., & Fink, G. R. (2009). End or means--the "what" and "how" of observed intentional actions. Journal of cognitive neuroscience, 21(4), 776–90. doi:10.1162/jocn.2009.21058

Hétu, S., Mercier, C., Eugène, F., Michon, P.-E., & Jackson, P. L. (2011). Modulation of brain activity during action observation: influence of perspective, transitivity and meaningfulness. (A. Sirigu, Ed.) PloS one, 6(9), e24728. doi:10.1371/journal.pone.0024728

Iacoboni, M., Koski, L. M., Brass, M., Bekkering, H., Woods, R. P., Dubeau, M. C., Mazziotta, J. C., et al. (2001). Reafferent copies of imitated actions in the right superior temporal cortex. Proceedings of the National Academy of Sciences of the United States of America, 98(24), 13995–9. doi:10.1073/pnas.241474598

Iacoboni, M. (2005). Neural mechanisms of imitation. Current opinion in neurobiology, 15(6), 632–7. doi:10.1016/j.conb.2005.10.010

Iacoboni, M. (2009). Imitation, empathy, and mirror neurons. Annual review of psychology, 60, 653–70. doi:10.1146/annurev.psych.60.110707.163604

Iacoboni, M., & Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. Nature reviews. Neuroscience, 7(12), 942–51. doi:10.1038/nrn2024

Iacoboni, M., Molnar-Szakacs, I., Gallese, V., Buccino, G., Mazziotta, J. C., & Rizzolatti, G. (2005). Grasping the intentions of others with one's own mirror neuron system. PLoS biology, 3(3), e79. doi:10.1371/journal.pbio.0030079

Jackson, P. L., Meltzoff, A. N., & Decety, J. (2006). Neural circuits involved in imitation and perspective-taking. NeuroImage, 31(1), 429–39. doi:10.1016/j.neuroimage.2005.11.026

Kang, S. S., Sponheim, S. R., Chafee, M. V, & MacDonald, A. W. (2011). Disrupted functional connectivity for controlled visual processing as a basis for impaired spatial working memory in schizophrenia. Neuropsychologia, 49(10), 2836–47. doi:10.1016/j.neuropsychologia.2011.06.009

Kato, Y., Muramatsu, T., Kato, M., Shibukawa, Y., Shintani, M., & Mimura, M. (2011). Magnetoencephalography study of right parietal lobe dysfunction of the evoked mirror neuron system in antipsychotic-free schizophrenia. PloS one, 6(11), e28087. doi:10.1371/journal.pone.0028087

Keysers, C., & Perrett, D. I. (2004). Demystifying social cognition: a Hebbian perspective. Trends in cognitive sciences, 8(11), 501–7. doi:10.1016/j.tics.2004.09.005

Kilner, J. M., Friston, K. J., & Frith, C. D. (2007). Predictive coding: an account of the mirror neuron system. Cognitive processing, 8(3), 159–66. doi:10.1007/s10339-007-0170-2

King, B. H., & Lord, C. (2011). Is schizophrenia on the autism spectrum? Brain research, 1380(null), 34–41. doi:10.1016/j.brainres.2010.11.031

Koski, L., Iacoboni, M., Dubeau, M.-C., Woods, R. P., & Mazziotta, J. C. (2003). Modulation of cortical activity during different imitative behaviors. Journal of neurophysiology, 89(1), 460–71. doi:10.1152/jn.00248.2002

Langdon, R., Ward, P. B., & Coltheart, M. (2010). Reasoning anomalies associated with delusions in schizophrenia. Schizophrenia bulletin, 36(2), 321–30. doi:10.1093/schbul/sbn069

Lee, T.-W., Josephs, O., Dolan, R. J., & Critchley, H. D. (2006). Imitating expressions: emotion-specific neural substrates in facial mimicry. Social cognitive and affective neuroscience, 1(2), 122–35. doi:10.1093/scan/nsl012

Lehrl, S., Triebig, G., & Fischer, B. (1995). Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurologica Scandinavica, 91(5), 335–345. doi:10.1111/j.1600-0404.1995.tb07018.x

Leube, D., Knoblich, G., Erb, M., Grodd, W., Bartels, M., & Kircher, T. T. (2003). The neural correlates of perceiving one's own movements. NeuroImage, 20(4), 2084–2090. doi:10.1016/j.neuroimage.2003.07.033

Lindner, A., Thier, P., Kircher, T. T. J., Haarmeier, T., & Leube, D. T. (2005). Disorders of agency in schizophrenia correlate with an inability to compensate for the sensory consequences of actions. Current biology : CB, 15(12), 1119–24.

doi:10.1016/j.cub.2005.05.049

Lotze, M., Heymans, U., Birbaumer, N., Veit, R., Erb, M., Flor, H., & Halsband, U. (2006). Differential cerebral activation during observation of expressive gestures and motor acts. Neuropsychologia, 44(10), 1787–95. doi:10.1016/j.neuropsychologia.2006.03.016

Macaluso, E., Frith, C. D., & Driver, J., (2000). Modulation of Human Visual Cortex by Crossmodal Spatial Attention. Science, 289(5482), 1206–1208. doi:10.1126/science.289.5482.1206

Maeda, T., Kato, M., Muramatsu, T., Iwashita, S., Mimura, M., & Kashima, H. (2012). Aberrant sense of agency in patients with schizophrenia: forward and backward over-attribution of temporal causality during intentional action. Psychiatry research, 198(1), 1–6. doi:10.1016/j.psychres.2011.10.021

Makris, N., Kennedy, D. N., McInerney, S., Sorensen, A. G., Wang, R., Caviness, V. S., & Pandya, D. N. (2005). Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cerebral cortex (New York, N.Y. : 1991), 15(6), 854–69. doi:10.1093/cercor/bhh186

Mané, A., Falcon, C., Mateos, J. J., Fernandez-Egea, E., Horga, G., Lomeña, F., Bargalló, N., et al. (2009). Progressive gray matter changes in first episode schizophrenia: a 4-year longitudinal magnetic resonance study using VBM. Schizophrenia research, 114(1-3), 136–43. doi:10.1016/j.schres.2009.07.014

Matthews, N., Gold, B. J., Sekuler, R., & Park, S. (2011). Gesture Imitation in Schizophrenia. Schizophrenia bulletin, sbr062–. doi:10.1093/schbul/sbr062

McCormick, L. M., Brumm, M. C., Beadle, J. N., Paradiso, S., Yamada, T., & Andreasen, N. (2012). Mirror neuron function, psychosis, and empathy in schizophrenia. Psychiatry research, 201(3), 233–9. doi:10.1016/j.pscychresns.2012.01.004

Mishkin, M., Ungerleider, L. G., & Macko, K. A. (1983). Object vision and spatial vision: two cortical pathways. Trends in Neurosciences, 6(null), 414–417. doi:10.1016/0166-2236(83)90190-X

Molenberghs, P., Brander, C., Mattingley, J. B., & Cunnington, R. (2010). The role of the superior temporal sulcus and the mirror neuron system in imitation. Human brain mapping, 31(9), 1316–26. doi:10.1002/hbm.20938

Molenberghs, P., Cunnington, R., & Mattingley, J. B. (2012). Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. Neuroscience and biobehavioral reviews, 36(1), 341–9. doi:10.1016/j.neubiorev.2011.07.004

Molinari, E., Baraldi, P., Campanella, M., Duzzi, D., Nocetti, L., Pagnoni, G., & Porro, C. A. (2012). Human Parietofrontal Networks Related to Action Observation Detected at Rest. Cerebral cortex (New York, N.Y. : 1991), bhr393–. doi:10.1093/cercor/bhr393

Molnar-Szakacs, I., Kaplan, J., Greenfield, P. M., & Iacoboni, M. (2006). Observing complex action sequences: The role of the fronto-parietal mirror neuron system. NeuroImage, 33(3), 923–35. doi:10.1016/j.neuroimage.2006.07.035

Mukamel, R., Ekstrom, A. D., Kaplan, J., Iacoboni, M., & Fried, I. (2010). Single-neuron responses in humans during execution and observation of actions. Current biology : CB, 20(8), 750–6. doi:10.1016/j.cub.2010.02.045

Newman-Norlund, R. D., van Schie, H. T., van Zuijlen, A. M. J., Bekkering, H. (2007). The mirror neuron system is more active during complementary compared with imitative action. Nature Neuroscience 10: 817–818. doi:10.1038/nn1911

Nichols, T., Brett, M., Andersson, J., Wager, T., & Poline, J. B. (2005). Valid conjunction inference with the minimum statistic. NeuroImage, 25 (3), 653–660. doi:10.1016/j.neuroimage.2004.12.005,

Park, K.-M., Kim, J.-J., Ku, J., Kim, S. Y., Lee, H. R., Kim, S. I., & Yoon, K.-J. (2009). Neural basis of attributional style in schizophrenia. Neuroscience letters, 459(1), 35–40. doi:10.1016/j.neulet.2009.04.059

Park, S., Matthews, N., & Gibson, C. (2008). Imitation, simulation, and schizophrenia. Schizophrenia bulletin, 34(4), 698–707. doi:10.1093/schbul/sbn048

Pavlidou, A., Schnitzler, A., & Lange, J. (2012). Interactions between visual and motor areas during the recognition of plausible actions as revealed by magnetoencephalography. Human brain mapping. doi:10.1002/hbm.22207

Pelphrey, K. A., Morris, J. P., Michelich, C. R., Allison, T., & McCarthy, G. (2005). Functional anatomy of biological motion perception in posterior temporal cortex: an FMRI study of eye, mouth and hand movements. Cerebral cortex (New York, N.Y. : 1991), 15(12), 1866–76. doi:10.1093/cercor/bhi064

Perkins, T., Stokes, M., McGillivray, J., & Bittar,

R. (2010). Mirror neuron dysfunction in autism spectrum disorders. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia, 17(10), 1239–43. doi:10.1016/j.jocn.2010.01.026

Pfeifer, J. H., Iacoboni, M., Mazziotta, J. C., & Dapretto, M. (2008). Mirroring others' emotions relates to empathy and interpersonal competence in children. NeuroImage, 39(4), 2076–85. doi:10.1016/j.neuroimage.2007.10.032

Powell, H. W. R., Guye, M., Parker, G. J. M., Symms, M. R., Boulby, P., Koepp, M. J., Barker, G. J., et al. (2004). Noninvasive in vivo demonstration of the connections of the human parahippocampal gyrus. NeuroImage, 22(2), 740–7. doi:10.1016/j.neuroimage.2004.01.011

Quintana, J., Davidson, T., Kovalik, E., Marder, S. R., & Mazziotta, J. C. (2001). A compensatory mirror cortical mechanism for facial affect processing in schizophrenia. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 25(6), 915–24. doi:10.1016/S0893-133X(01)00304-9

Rizzolatti, G., Fogassi, L., & Gallese, V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. Nature reviews. Neuroscience, 2(9), 661–70. doi:10.1038/35090060

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. Annual review of neuroscience, 27, 169–92. doi:10.1146/annurev.neuro.27.070203.144230

Rizzolatti, G., & Fabbri-Destro, M. (2008). The mirror system and its role in social cognition. Current opinion in neurobiology, 18(2), 179–84. doi:10.1016/j.conb.2008.08.001

Rizzolatti, G., & Fabbri-Destro, M. (2010). Mirror neurons: from discovery to autism. Experimental brain research. Experimentelle Hirnforschung. Expérimentation cérébrale, 200(3-4), 223–37. doi:10.1007/s00221-009-2002-3

Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. Cognitive Brain Research, 3(2), 131–141. doi:10.1016/0926-6410(95)00038-0

Rizzolatti, G., & Sinigaglia, C. (2010). The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. Nature reviews. Neuroscience, 11(4), 264–74. doi:10.1038/nrn2805

Schendan, H. E., & Stern, C. E. (2008). Where vision meets memory: prefrontal-posterior networks for visual object constancy during categorization and recognition. Cerebral cortex (New York, N.Y. : 1991), 18(7), 1695–711. doi:10.1093/cercor/bhm197

Schippers, M. B., & Keysers, C. (2011). Mapping the flow of information within the putative mirror neuron system during gesture observation. NeuroImage, 57(1), 37–44. doi:10.1016/j.neuroimage.2011.02.018

Schmitt, A., Hasan, A., Gruber, O., & Falkai, P. (2011). Schizophrenia as a disorder of disconnectivity. European archives of psychiatry and clinical neuroscience, 261 Suppl , S150–4. doi:10.1007/s00406-011-0242-2

Schultz, C. C., Koch, K., Wagner, G., Roebel, M., Nenadic, I., Gaser, C., Schachtzabel, C., et al. (2010). Increased parahippocampal and lingual gyrification in first-episode schizophrenia. Schizophrenia research, 123(2-3), 137–44. doi:10.1016/j.schres.2010.08.033

Schürmann, M., Järveläinen, J., Avikainen, S., Cannon, T. D., Lönnqvist, J., Huttunen, M., & Hari, R. (2007). Manifest disease and motor cortex reactivity in twins discordant for schizophrenia. The British journal of psychiatry : the journal of mental science, 191(2), 178–9. doi:10.1192/bjp.bp.106.024604

Shih, P., Shen, M., Ottl, B., Keehn, B., Gaffrey, M. S., & Müller, R.-A. (2010). Atypical network connectivity for imitation in autism spectrum disorder. Neuropsychologia, 48(10), 2931–9. doi:10.1016/j.neuropsychologia.2010.05.035

Sprong, M., Schothorst, P., Vos, E., Hox, J., & Van Engeland, H. (2007). Theory of mind in schizophrenia: meta-analysis. The British journal of psychiatry : the journal of mental science, 191, 5–13. doi:10.1192/bjp.bp.107.035899

Stephan, K. E., Friston, K. J., & Frith, C. D. (2009). Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophrenia Bulletin, 35, 509–527. doi: 10.1093/schbul/sbn176.

Synofzik, M., Thier, P., Leube, D. T., Schlotterbeck, P., & Lindner, A. (2010). Misattributions of agency in schizophrenia are based on imprecise predictions about the sensory consequences of one's actions. Brain : a journal of neurology, 133(Pt 1), 262–71. doi:10.1093/brain/awp291

Tomassini, V., Jbabdi, S., Klein, J. C., Behrens, T. E. J., Pozzilli, C., Matthews, P. M., Rushworth,

M. F. S., et al. (2007). Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. The Journal of neuroscience : the official journal of the Society for Neuroscience, 27(38), 10259–69. doi:10.1523/JNEUROSCI.2144-07.2007

Turella, L., Pierno, A. C., Tubaldi, F., & Castiello, U. (2009). Mirror neurons in humans: consisting or confounding evidence? Brain and language, 108(1), 10–21. doi:10.1016/j.bandl.2007.11.002

Van der Gaag, C., Minderaa, R. B., & Keysers, C. (2007). Facial expressions: what the mirror neuron system can and cannot tell us. Social neuroscience, 2(3-4), 179–222. doi:10.1080/17470910701376878

Van Overwalle, F., & Baetens, K. (2009). Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. NeuroImage, 48(3), 564–84. doi:10.1016/j.neuroimage.2009.06.009

Varcin, K. J., Bailey, P. E., & Hendry, J. D. (2010). Empathic deficits in schizophrenia: The potential role of rapid facial mimicry. Journal of the International Neuropsychological Society, 16(04), 621–629. Retrieved from http://journals.cambridge.org/abstract_S1355617710000329

Villalobos, M. E., Mizuno, A., Dahl, B. C., Kemmotsu, N., & Müller, R.-A. (2005). Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism. NeuroImage, 25(3), 916–25. doi:10.1016/j.neuroimage.2004.12.022

Weissman, D. H., Perkins, A. S., & Woldorff, M. G. (2008). Cognitive control in social situations: a role for the dorsolateral prefrontal cortex. NeuroImage, 40(2), 955–62. doi:10.1016/j.neuroimage.2007.12.021

Wild, B., Erb, M., Eyb, M., Bartels, M., & Grodd, W. (2003). Why are smiles contagious? An fMRI study of the interaction between perception of facial affect and facial movements. Psychiatry Research: Neuroimaging, 123(1), 17–36. doi:10.1016/S0925-4927(03)00006-4

Williams, J. H. G., Waiter, G. D., Gilchrist, A., Perrett, D. I., Murray, A. D., & Whiten, A. (2006). Neural mechanisms of imitation and "mirror neuron" functioning in autistic spectrum disorder. Neuropsychologia, 44(4), 610–21. doi:10.1016/j.neuropsychologia.2005.06.010

Wittchen, H. U., Wunderlich, U, Gruschwitz, S, Zaudig, M. (1997). Strukturiertes Klinisches Interview für DSM-IV (SKID). Göttingen, Hogrefe: Interviewheft und Beurteilungsheft.

Woods, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. The Journal of clinical psychiatry, 64(6), 663–7. doi:10.4088/JCP.v64n0607

Wurm, M. F., Von Cramon, D. Y., & Schubotz, R. I. (2011). Do we mind other minds when we mind other minds' actions? A functional magnetic resonance imaging study. Human brain mapping, 32(12), 2141–50. doi:10.1002/hbm.21176

Supplement material

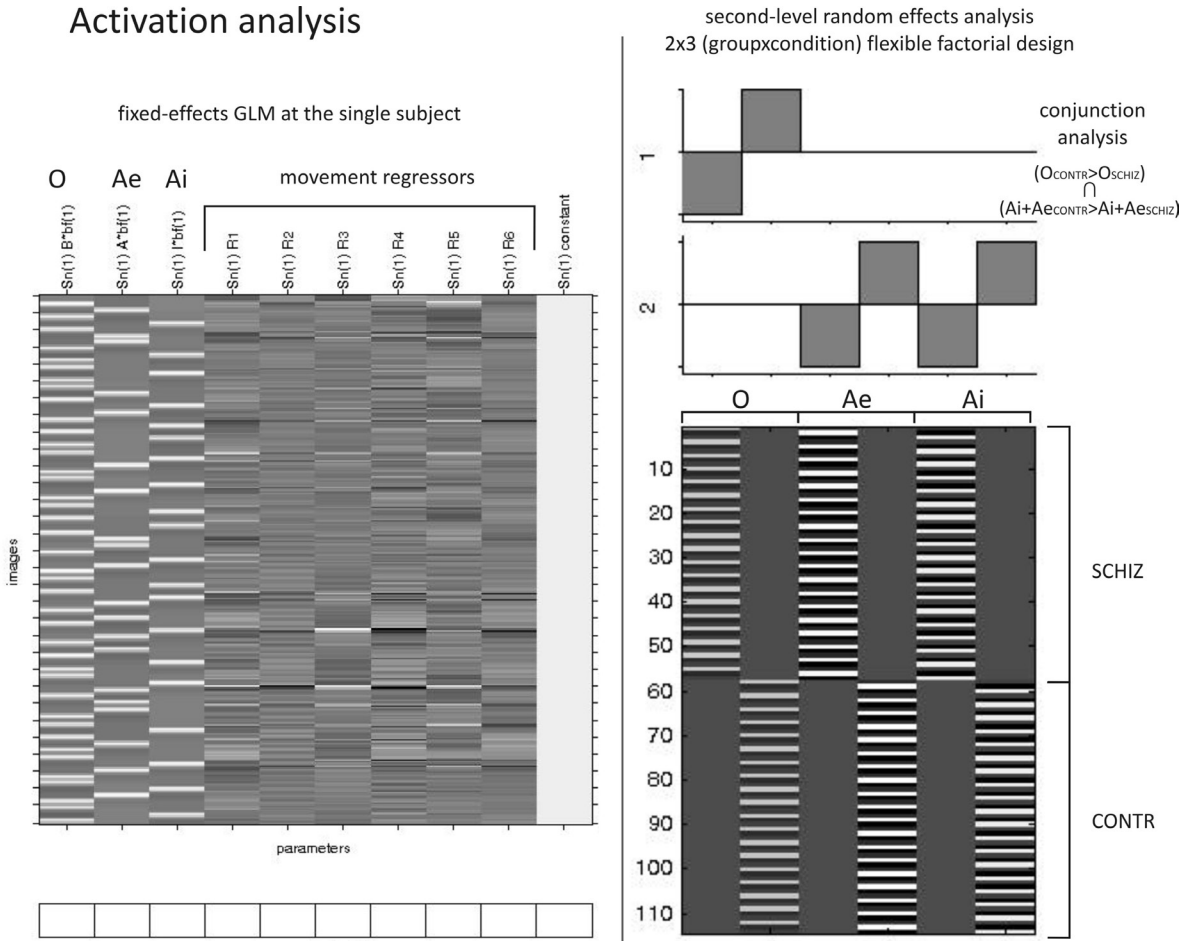

Figure 1.: Design matrix of the fixed-effects GLM exemplarily for one subject (left side) and the second-level group analysis (right side) for task activation analysis. *We included three conditions: observation (O), specific imitation (Ai) and execution (Ae) of grasp-movements. Additionally, the movement regressors were considered. Contrast images were calculated for activation as response to O, Ai, and to Ae respectively, compared to the unmodelled baseline activation (ISI). The contrast images of the participants were entered in a 2x3 (group x task) flexible factorial design. The contrast weights in the upper right indicate the performed conjunction analysis.*

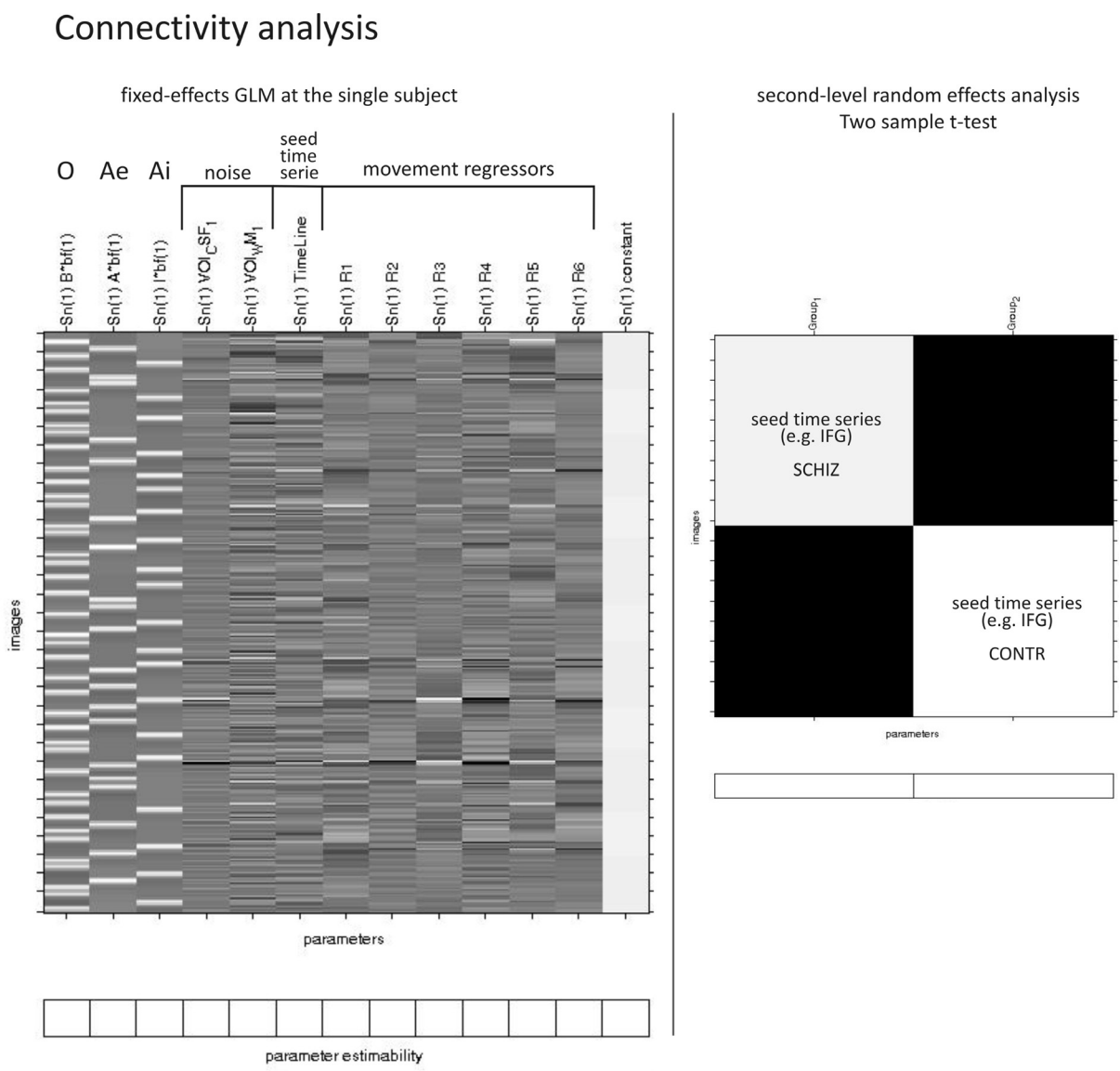

Figure 2.: Design matrix of the fixed-effects GLM exemplarily for one subject (left side) and the second-level group analysis (right side) for functional connectivity analysis. *We extracted the time series of the IFG and IPL seeds individually and corrected for task-related variance. Besides the time series, the movement regressors, noise (white matter and cerebrospinal liquid time series) and three conditions (O, Ai, Ae) were entered in the design matrix. Correlations between seed time series and each voxel in the brain were examined. The connectivity map for every participant was generated and compared across groups (schizophrenia SCHIZ, controls CONTR) in a second-level analysis using two-sample t-tests for seeds (e.g., IFG) individually.*

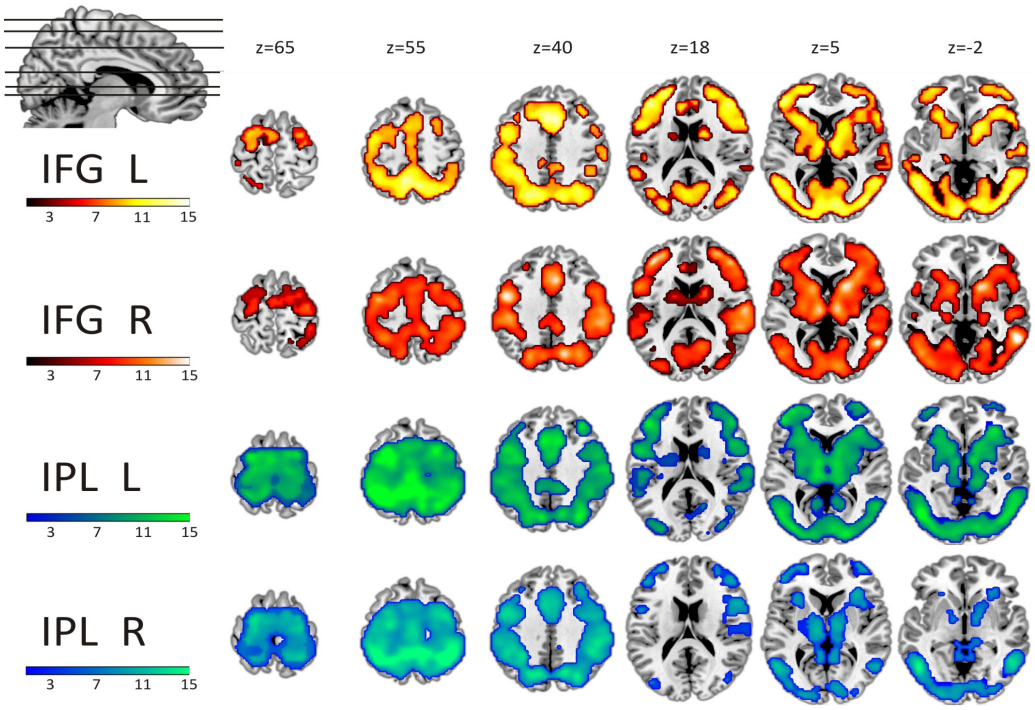

Figure 3.: Functional connectivity from MNS seeds to the rest of the brain. *Whole brain functional connectivity maps from chosen seeds in healthy controls for the inferior frontal gyrus (IFG, BA 44) in the left (yellow) and in the right hemisphere (red), for the inferior parietal lobe (IPL) in the left (green), and in the right hemisphere (blue). For illustrational purposes we chose a threshold at T>6. Colour bars show the corresponding T-value. Black lines through the brain in the upper left show selected slices.*

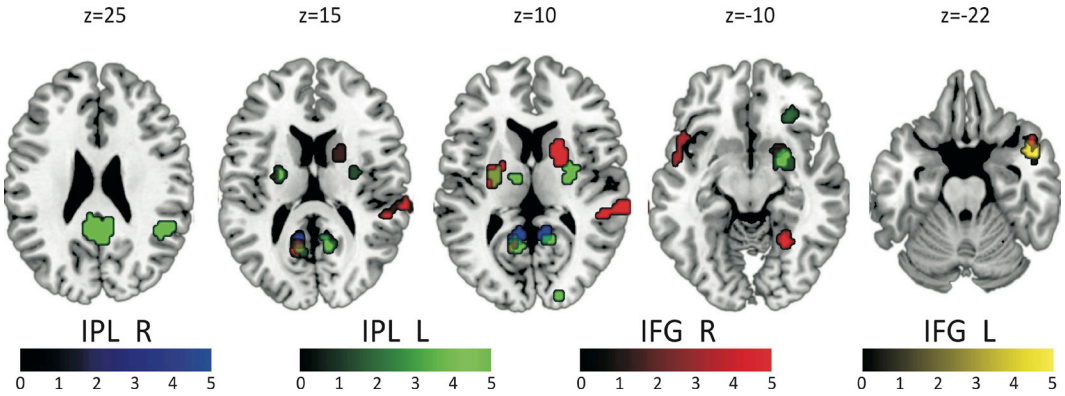

Figure 4.: Comparison between whole brain functional connectivity maps from IPL and IFG seeds of healthy controls versus patients with schizophrenia (CONTR>SCHIZ): *Differences in connectivity were found between the right IPL (***blue***) and medial calcarine gyrus (BA 18) extending in hippocampal regions, between the left IPL (***green***) and higher visual associative areas (including cuneus, LNG), basal ganglia (pallidum, putamen, caudate), thalamus, parts of the limbic system system (cingulate cortex), and most importantly to right IFG, right middle and superior temporal gyrus, supramarginal gyrus and precuneus. The right IFG seed (***red***) showed decreased synchrony in schizophrenia with e.g., the STS, bilateral temporal pole, putamen, thalamus and visual areas (fusiform gyrus, calcarine), right parahippocampus and precuneus. The left IFG connectivity (***yellow***) show differences between groups primarily within the anterior right STS and temporal pole. P's<.05 FWE corr.*

Table 1. *Areas involved in observation-execution matching*

	Area	L/R	MNI coordinates			Cluster size	T value	Peak level p FWE corr.
			x	y	z			
CONTR								
1	Inferior Parietal Lobule	L	-33	-43	49	10503	13.57	0.000
	Postcentral Gyrus (BA 2)	R	42	-43	61		12.16	0.000
	Fusiform Gyrus	R	39	-52	-20		11.18	0.000
	Thalamus	L	-21	-25	-2		11.00	0.000
	Fusiform Gyrus	R	39	-67	-17		10.95	0.000
	Fusiform Gyrus	L	-39	-67	-17		10.86	0.000
	Precuneus (SPL)	R	12	-64	61		10.49	0.000
	Lingual Gyrus	R	9	-52	1		10.39	0.000
	Middle Temporal Gyrus	R	54	-52	-2		10.28	0.000
	Precuneus (SPL)	R	6	-52	55		9.51	0.000
2	Precentral Gyrus	L	-30	-4	61	465	9.00	0.000
		L	-54	2	37		7.84	0.000
3	Superior Frontal Gyrus	R	33	-4	61	309	9.54	0.000
4	Superior Temporal Gyrus (IPC)	R	60	-37	19	165	9.45	0.000
5	SMA (BA 6)	L	0	11	49	60	6.72	0.000
	Middle Cingulate Cortex	L	-6	23	37		5.64	0.001
6	Middle Frontal Gyrus	R	45	35	22	46	6.96	0.000
	Inferior Frontal Gyrus	R	42	32	25		6.89	0.001
7	SMA (BA 6)	L	0	2	67	9	5.90	0.000
8	Middle Frontal Gyrus	L	-36	35	31	5	5.82	0.000
	Middle Frontal Gyrus (BA 44)	L	-33	32	22		5.67	0.001
SCHIZ								
1	Superior Parietal Lobule	R	36	-43	58	691	9.81	0.000
		R	21	-55	61		8.42	0.000
		R	24	-64	52		7.28	0.000
2	Inferior Occipital Gyrus	L	-45	-67	-5	661	7.97	0.000
	Middle Temporal Gyrus	L	-51	-70	7		7.97	0.000
	Fusiform Gyrus	L	-39	-58	-20		7.87	0.000
3	Inferior Parietal Lobule	L	-36	-43	49	463	10.52	0.000
	Superior Parietal Lobule	L	-30	-55	61		8.98	0.000
4	Middle Temporal Gyrus	R	54	-52	1	452	7.84	0.000
	Inferior Temporal Gyrus	R	51	-58	-5		7.80	0.000
	Fusiform Gyrus	R	36	-52	-17		7.33	0.000
5	Middle Frontal Gyrus	R	33	-1	58	164	8.48	0.000
6	Thalamus	L	-21	-25	-2	151	8.43	0.000
7	Precentral Gyrus (incl. BA 6)	L	-27	-10	55	90	7.91	0.000
8	Thalamus	R	18	-25	1	53	7.32	0.000
9	Superior Temporal Gyrus (IPC)	R	54	-37	19	19	6.84	0.000
10	Precentral Gyrus (incl. BA 6, 44)	R	51	8	31	15	6.00	0.000
		R	54	5	40		5.90	0.000
11	Precentral Gyrus (incl. BA 6, 44)	L	-54	5	34	11	6.27	0.000
12	Superior Temporal Gyrus (IPC)	L	-60	-40	19	10	6.07	0.000

k>5, p<.001 FWE corr., T>5.57 ~FWE .001; L/R indicates the hemisphere (left/right)

Table 2. *Reduced functional connectivity in schizophrenia between IFG and IPL seeds and areas around the lingual gyrus (BA 18, 27, 29; 30)*

Seeds	Associated areas	L/R	MNI coordinates			Cluster size	T value	peak level p FWE corr.
			x	y	z			
IFG right								
1	Calcarine Gyrus	L	-15	-58	10	56	5.45	0.002
2	Precuneus	R	9	-52	13	47	5.29	0.003
3	Calcarine Gyrus	R	18	-88	10	44	4.90	0.008
		R	9	-79	13		4.56	0.019
4	Calcarine Gyrus	R	6	-82	7	19	4.59	0.018
		L	-3	-79	7		4.41	0.027
	Lingual Gyrus	**L**	**-6**	**-79**	**1**		**4.26**	**0.027**
5	Superior Occipital Gyrus	L	-15	-94	13	7	4.50	0.022
6	Fusiform Gyrus	L	-33	-70	-11	4	4.50	0.022
7	Calcarine Gyrus	L	-12	-70	16	3	4.24	0.042
8	**Lingual Gyrus**	**R**	**12**	**-79**	**1**	**3**	**4.29**	**0.037**
IFG left								
1	Middle Occipital Gyrus	L	-21	-91	10	13	4.96	0.007
	Superior Occipital Gyrus	L	-15	-97	10		4.70	0.013
2	Inferior Occipital Gyrus	R	33	-85	-2	9	5.00	0.006
3	Middle Occipital Gyrus	L	-33	-85	-2	3	4.28	0.037
IPL right								
1	Calcarine Gyrus	L	-9	-52	4	249	6, 26	0.000
	Lingual Gyrus	**R**	**9**	**-49**	**4**		**6, 21**	**0.000**
	Hippocampus (CA)	R	15	-34	1		5,05	0.005
IPL left								
1	Calcarine Gyrus	L	-12	-55	7	289	6.11	0.000
	Lingual Gyrus	**R**	**12**	**-52**	**7**		**5.60**	**0.001**
	Hippocampus (SUB)	R	18	-34	-5		5.15	0.004
2	Cuneus	R	21	-91	10	45	5.27	0.003
	Calcarine Gyrus	R	6	-85	4		5.13	0.005
	Lingual Gyrus	**L**	**-9**	**-85**	**-8**		**4.48**	**0.024**
3	Middle Occipital Gyrus	L	-33	-85	-2	37	5.63	0.001
	Fusiform Gyrus	L	-21	-82	-8		4.61	0.017
		L	-27	-76	-8		4.37	0.032
4	**Lingual Gyrus**	**R**	**18**	**-79**	**-2**	**29**	**4.74**	**0.013**
	Fusiform Gyrus	R	24	-76	-11		4.63	0.017
5	Calcarine Gyrus	R	21	-91	4	11	5.43	0.002
	Inferior Occipital Gyrus	R	30	-85	-2		4.51	0.022
6	Superior Occipital Gyrus	L	-15	-91	10	4	4.56	0.020

Seeds highlighted in green, ROI mask consists of BA 18, 27, 29; 30; CONTR>SCHIZ, nSCHIZ=19, nCONTR=19, L/R indicates the hemisphere, p<.05 FWE corr. equates T>4.15, k≥3

Dysconnectivity of the inferior frontal gyrus: implications for an impaired self-other distinction in patients with schizophrenia*

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Manuskript #3

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Abstract

Ego-disturbances in schizophrenia might be caused by a failure of the efference copy mechanism, which compares efferent with reafferent signals and attenuates the sensory consequences of self-produced movements. We run a functional magnetic resonance imaging study, measuring 16 patients with schizophrenia and 16 healthy matched controls while performing both intentional and unintentional continuous hand-movements in two consecutive experiments. Periodically we varied the delay of visual feedback to create a sensory-motor discrepancy. Exclusively for intentional movements the activation pattern of the inferior frontal gyrus (IFG) in patients was opposite to that of controls: less attenuated during time-congruent feedback and less activated during time-incongruent feedback. Additionally, several functional connections within the mismatch detection network (IFG with insula, putamen, medial orbitofrontal cortex) were affected. Also, activity of the dysconnected orbitofrontal cortex was correlated with ego-disturbance in patients. We discuss that in healthy individuals the IFG might enable a distinction between self and non-self using time-characteristics of feedback, whereas in patients this sensory mismatch detection is altered. Moreover, due to the dysconnectivity of the IFG, the efferent and reafferent signal exchange between perceptual and motor areas seems to be affected. This might cause self-monitoring deficits in patients, which contributes to the emergence of ego-disturbances.

Keywords: Efference copy I Agency I Inferior Frontal Gyrus I Schizophrenia I fMRI I Functional Connectivity

Introduction

An organism has to take into account the sensory consequences of its own actions. This is important to distinguish sensory input that results from own movements (e.g., eye motion), from the sensory signals that are produced by outside forces (e.g., a wild beast). Our neural architecture encompasses an evolutionary preserved mechanism called efference copy mechanism to solve this task. This mechanism has originally been postulated to explain the compensation of the sensory consequences of one's own eye movements, i.e. the perception of a stable environment despite of the retinal shift during smooth pursuit (Von Holst and Mittelstaedt, 1950; Sperry, 1950). This concept has been extended on other motor-sensory loops (for a review see Pynn and DeSouza, 2013), e.g., error monitoring while executing goal-directed actions (Wolpert et al., 1995), and has been experimentally confirmed in several species (e.g., crickets, birds, electric fish; see Crapse and Sommer, 2008). It is suggested that while planning an action, an efference copy of the motor command is built and sent as a "corollary discharge" signal to the corresponding sensory brain areas, suppressing the perception of impending sensations that result from this self-initiated action by modulating cortical responsiveness (reviews in Cullen, 2004; Pynn and DeSouza, 2013). Moreover, it has been hypothesised that a mismatch detection system located in the parietal lobe compares actual sensory feedback with expected feedback (Frith et al., 2000, Frith, 2005), and may contribute to the processing of the sense of agency in a higher cortical centre, i.e. the prefrontal cortex (Synofzik et al., 2008).

As the concept of the efference copy mechanism taps into the distinction between the internal self and the external world it became of interest for research in the pathogenesis of schizophrenia, a disease that is partly defined by symptoms that suggest a higher permeability or breakdown of this border in so called delusions of influence or passivity phenomena (ego-disturbances) during which the patients report external influences on their thoughts, movements or inner sensations (Andreasen and Olsen, 1982; Leube et al., 2008).

The disturbed sense of agency and its relation to hallucinations and delusions of influence in schizophrenia has been explained by an inability to predict the sensory consequences of one's actions due to a failure of the efference mechanism, either in generating corollary discharge or receiving and integrating these signals in addressed sensory cortices (e.g., Blakemore et al., 2000; Feinberg, 1978; Ford and Mathalon, 2004; Frith et al., 2000). First empirical data that back this hypothesis came from psychophysical experiments (Lindner et al., 2005) but it remained largely unclear what the neural correlate of this deficit is and whether a dysconnectivity interferes with the necessary signal exchange between motor and sensory cortices to compare efferent and afferent feedback. Interestingly, Haggard et al. (2002) concluded in their study on healthy participants that the impoverished agency attribution seen in schizophrenia may underlay an altered "intentional binding" effect (i.e. the matching of action and effect based on temporal predictability and contiguity). Furthermore, the authors described these effects as exclusively for intentional, voluntary action. Therefore, in the two present functional magnetic resonance imaging (fMRI) experiments we compared patients with schizophrenia and healthy controls while performing two different motor tasks. They either performed an intentional, goal directed movement with a chess figure or they performed an unintentional movement of their hand (open-close). The visual feedback of the movement via video camera and computer screen was manipulated by being presented either with (200 ms) or without a time delay. The delayed feedback creates a sensory-motor discrepancy between the normally congruent efferent and reafferent signals, at least in healthy participants. Additionally, this procedure is known to elicit an illusion of a disturbed sense of agency and allows the investigation of the mismatch detection system (Leube et al., 2003a). Furthermore, since agency attributions mostly underlie unconscious automatic mechanisms (Jeannerod and Pacherie, 2004), we addressed the automatic or implicit feeling of being the agent of an action rather than typically explicit judgement of agency (see distinction in Synofzik et al., 2008) in this study. For the comparison of activation patterns between patients and matched controls, we defined three important regions of interest that have often been shown to be related to the processing or the loss of self-agency, namely the posterior sulcus temporalis superior (STS, e.g., Leube et al., 2003a; Nahab et al., 2011), the left putamen (Leube et al., 2003a;2010) and the right inferior frontal gyrus (IFG; e.g., Fink et al., 1999; Leube et al., 2003a,b; Nahab et al., 2011). We hypothesized that the neural activation in these regions differs during the task performance in patients with schizophrenia compared to controls – with presumably less attenuation while perceiving time-congruent feedback and a lack of modulation in response to temporal-delayed feedback. Upgrading the earlier experiment by Leube et al. (2010) by using additionally intentional movements, we hypothesized – in line with Haggard et al.'s (2002) reasoning - that this effect is more pronounced in schizophrenia while performing goal directed, intentional movements than while performing movements without a goal. While Leube et al. (2010) showed altered activation only for the putamen in schizophrenia, we expected that our modification of the study design allows a more elaborate investigation of the aforementioned regions involved in self-agency. Furthermore, keeping in mind that the model of the efference copy mechanism involves a large-scale signal exchange between motor and sensory cortices, the additional aim of the study was to clarify whether a broader dysconnectivity may underlie the self-monitoring deficits in patients. We hypothesized that a dysconnectivity prevents corollary discharge of motor-related perceptual areas (e.g., IFG) normally caused by brain regions that predict sensory consequences of planned actions (e.g., putamen, Leube et al., 2003a).

Materials and Methods

2.1. Participants

Nineteen patients (one female, 18 males; all right-handed as assessed by the Edinburgh Handedness Inventory by Oldfield, 1971) diagnosed with schizophrenia (SCHIZ, without comorbid psychiatric disorders) according to DSM-IV criteria (American Psychiatric Association, 1994) by two independent psychiatrists using patient and relative interviews as well as past and present chart notes were included in the study. Three patients were excluded from the data analysis because two of them were not capable to perform the task inside the scanner according to the instructions and one did not complete the fMRI data acquisition. All patients were taking medication at the time of the study. A total of 16 healthy controls (CONTR, 1 female, 15 males; all right-handed) without a history of psychiatric, neurological or medical diagnoses or first-degree relatives with psychotic illnesses took part in the study. To ensure the absence of psychiatric disorders the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen et al., 1996) was conducted. Healthy controls were matched to the patient group on the basis of sex, age and education (see Table 1) and we included only individually matched control participants. All subjects had normal vision and hearing. The study was approved by the local ethics committee of the Medical Faculty of the University of Marburg. All subjects gave written informed consent.

2.2. Assessment instruments

In patients we assessed psychiatric symptoms using the Scales for the Assessment of Positive Symptoms (SAPS, Andreasen, 1984) and Negative Symptoms (SANS, Andreasen, 1983). General intelligence was estimated using a German vocabulary test, the Mehrfachwahl-Wortschatz-Intelligenztest (Multiple Choice Word Test, MWT-B) (Lehrl et al., 1995).

2.3. Stimulus construction

During the first experiment, subjects performed a goal directed/intentional movement (INT). They were moving a chessman continuously from the middle field of a 3x3 “mini chessboard” to the front and backwards (1 Hz) while BOLD (i.e. blood oxygen level dependent) contrast was measured with fMRI (Figure 1A). In order to maintain the intentionality over the period of the experiment, participants replaced

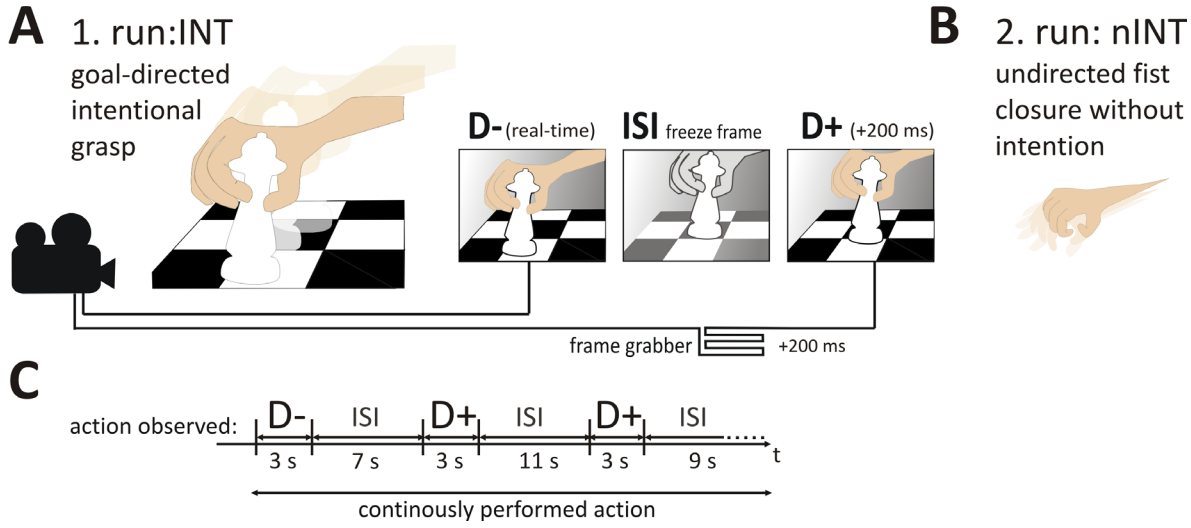

Figure 1.: Schematic representation of the stimulus and feedback presentation. *During fMRI two runs were performed: (**A**) continuous goal-directed hand movements with intentional object interaction (INT) and (**B**) continuous undirected hand closure (nINT). (**C**) Illustration of experimental trials: the own visual feedback was presented in real-time (D-) or with an introduced temporal delay of 200 ms (D+). A baseline condition (ISI) was shown between the stimuli.*

Table 1: *Demographic and clinical characteristics of study participants*

	SCHIZ (n=16)	***CONTR (n=16)***	***Statistics***
Mean age (years)	31.1 ± 8.0	29.6 ± 7.1	n.s.
Male to female ratio	15:1	15:1	-
Intelligence (MWT-B)	109.3 ± 17.0	107.4 ± 14.1	n.s.
Mean duration of Illness (years)	8.3 ± 6.8	-	-
Mean CPZ equivalents (mg/day)	742.6 ± 574.7	-	-
SANS total	21.5 ± 19.2	-	-
SAPS total	17.1 ± 12.3	-	-
Subscale ego-disturbance (mean of 5 items)	3.5 ± 4.5		

Patients with schizophrenia (SCHIZ); control subjects (CONTR); ± indicates the standard deviation; chlorpromazine equivalent dose (CPZ), Scale for the Assessment of Negative Symptoms (SANS); Scale for the Assessment of Positive Symptoms (SAPS); SAPS rating for ego-disturbance comprises following items: delusions of being controlled (15), delusions of mind reading (16), thought broadcasting (17), thought insertion (18), thought withdrawal (18) (c.f. Schnell et al., 2008)

the chessman to the middle field between consecutive displacements and grasp again.

In the consecutive second experiment subjects performed an undirected/unintentional movement (nINT). They opened and closed their right hand continuously (1 Hz) and smoothly (Figure 1B; cf. Leube et al., 2003a) without any goal. Other than the action in the first experiment, a continuous fist closure is a meaningless gesture and rather uncommon in our daily routine. In the closing position, the fingers did not touch each other or the palm in order to minimize additional proprioceptive feedback. Previously, both procedures were practiced to ensure that participants were able to perform the actions correctly. Additionally, the experimenter visually monitored the individual performance during the experiments. The hand movements were filmed using an fMRI compatible video camera (Wild et al., 2000) and projected online onto a LCD screen, which subjects were able to see through a mirror (Figure 1A). This direct visual feedback of the own hand movement was given at random time points for a duration of three seconds. During these three-second trials, either a temporal delay of 200 ms (D+) was introduced or not (D-) according to a pseudo-random sequence. A total of 40 trials were performed (i.e., 20 trials with delay, 20 trials without). Between trials, the last image frame was frozen, so that subjects saw their static hand while they continued their movement. This baseline was jittered between 7 and 11 s (mean 8.9 s) (Figure 1C, ISI).

2.4. FMRI data acquisition

Participants were scanned at 3T MR scanner (Siemens Trio, Erlangen, Germany) with 36 near-axial slices and a distance factor of 10 % providing whole brain coverage. An echo planar imaging (EPI) sequence was used for acquisition of 230 functional volumes per run during the experiment (repetition time = 2.19 s, echo time = 30 ms, flip angle = 90°, slice thickness = 3 mm, field of view = 192 mm, voxel resolution = 3 x 3 x 3 mm). After the two functional runs, an anatomical high-resolution T_1-weighted 3-D scan was acquired (repetition time = 1.9 s, echo time = 2.52 ms, flip angle = 9°, slice thickness = 1 mm, field of view = 256 mm, voxel resolution = 1 x 1 mm, inter-slice gap = 0.5 mm).

2.7. FMRI data analysis

Functional MRI data were analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.5 (Mathworks Inc., Sherborn, Mass., USA). To correct for head movement artifacts the functional images were realigned for each subject to the mean image (using the default

unwarp and realign function). All EPI images were corrected for a temporal shift in acquisition (slice timing). Additionally, the resulting mean EPI image from the unwarp process was co-registered with the high-resolution structural T_1 image. Subsequently, images were segmented and the revealed parameters were used for spatial normalization to the standard stereotactic space defined by the Montreal Neurological Institute (MNI) template and resliced with a voxel size of 3×3×3 mm. Afterwards, they were spatially smoothed using a 10 mm full width at half maximum (FWHM) isotropic Gaussian kernel to accommodate intersubject variation in brain anatomy, and high-pass filtered at 1/100 Hz to remove low frequency drifts.

Task activation analysis

For the analyses we used a fixed-effect general linear model (GLM) at the single subject level including two regressors for the two conditions (D+, D-) convolved with the hemodynamic response function and the motion regressors. The single subject analysis for the two runs (INT, nINT) was performed separately. Contrast images were calculated for activation in the condition with delayed feedback (D+) and for the condition without delayed feedback (D-) compared to the baseline activation (frozen frame).

In a second-level random effects analysis, the individual contrast images from both runs (INT, nINT) were then entered into a 2x4 (group x condition) flexible factorial design to calculate differences in activation patterns between subjects and tasks, a statistical interaction [($D+_{CONTR}$ relative to $D-_{CONTR}$) relative to ($D+_{SCHIZ}$ relative to $D-_{SCHIZ}$)] in particular. The locations of the activation maxima were reported as MNI-coordinates (Brett et al., 2002) and family-wise error-corrected (FWE $p<.05$) on the cluster level. Region of interest (ROI) analyses were performed using the same regions as reported in Leube et al. (2003a), who conducted a similar experiment as ours (exp. 2, fist closure). They found a processing of delayed visual feedback related to the right posterior STS (sphere of 10 mm at [48 -42 18]), the left putamen and the IFG (for putamen and IFG neuroanatomical labels were used that are provided by Wake Forest Pick Atlas toolbox for SPM 8; http://fmri.wfubmc.edu), that processed a harsh mismatch between observed and performed action (Leube et al., 2003b).

Task-related and unrelated functional connectivity analysis

To address the hypothesis of an altered connectivity of underlying neural networks in patients with schizophrenia, we additionally studied functional connectivity with two different approaches. We measured task/delay-specific changes in the relationship between activities in different brain areas, using a psychophysiological interaction analysis (PPI, Friston et al., 1997). In the PPI analysis we examined the temporal correlation (physiological variable) between a seed region and the rest of the brain in the context of the specific task (psychological variable). Additionally, we applied a seed-voxel analysis without task effects. The difference between both approaches lay in the informative value. The seed voxel approach reveals statistical relations between regions through activation pattern similarities irrespective of time-characteristic of the visual feedback, whereas PPI gives information about how the delayed feedback affects the connection of brain areas in particular. A comparison of the connectivity maps of CONTR versus SCHIZ - revealed by PPI - could provide evidence for a putative disconnected mismatch network in SCHIZ in particular, whereas the seed voxel approach examines the self-monitoring network in general. Therefore, the additional benefit of PPI is the improved assessment of the source of a putative impaired processing of mismatch between time-incongruent feedback and currently performed actions in schizophrenia.

For both approaches (PPI and seed-voxel) we chose the group peak voxel activity of the inferior frontal gyrus (IFG, pars opercularis) at MNI-coordinates [42 11 31] on the basis of the main result from the statistical interaction of task by group in all participants. Starting at these peak activations on the group level, we identified the next local maximum within

each subject (in clusters exceeding 5 voxels) to account for interindividual alterations in activation patterns for the delay condition (D+>ISI, p<0.05 uncorrected). We limited this procedure by using a restriction to an IFG mask (using Wake Forest Pick Atlas toolbox for SPM 8; http://fmri.wfubmc.edu). Second, we extracted individual time series from the seed region in a sphere of a 5 mm radius. For the seed approach we corrected the extracted time series for task-related variance by setting an F-contrast on the six movement parameters. To account for noise, white matter and cerebrospinal fluid time series were extracted. The PPI time series were mean-corrected, high-pass filtered (f < 1/100) and adjusted for movement regressors.

Third, we built a new first level design matrix for both approaches separately to describe brain connectivity of the seed region with the entire, individual brain. For the seed-approach we included the seed time series, task, noise and movement regressors and set the T-contrast on the time series to generate individual connectivity maps. Correlations between seed time series and each voxel in the brain were examined according to Bedenbender et al. (2011). The PPI design matrix consisted of three columns: the contrast of two conditions (D+>D-, psychological), a time-series of the IFG (physiological), and an interaction variable that represents the interaction of the psychological and physiological variables. The latter interaction term (PPI regressor) is the element-by-element product of the time series and a vector coding for the main effect of task (i.e., 1 D+, −1 for D-). Regions that are stronger contextually connected with the IFG during the mismatch condition D+ than during D- were determined by testing for positive slopes of the PPI regressor (i.e., set a t-contrast on the PPI regressor).

Fourth, we performed second-level group analyses for both approaches separately. In both approaches we included the resulting β-maps or the PPI interaction term respectively in a two-sample t-test design and analyzed changes in either PPI or seed-voxel connectivity between groups. In the task-unrelated connectivity analysis, in which the delay should not play any role, we performed ROI-analyses in regions that slightly deviated from the ROIs in the activation analysis, because they are known to be activated irrespectively of delay length in a comparable feedback-task (Leube et al., 2003a; i.e., insula, precentral gyrus, supplementary motor area, putamen, postcentral gyrus).

To determine the possible relations between altered connectivity and ego-disturbance in patients, we performed correlation analyses using SPSS 21.0 for Windows. More precisely, we analyzed the relationship between the first eigenvariate of the significantly differentially connected clusters (revealed in the PPI approach) in patients and the respective scores of the ego-disturbance subscale of the SAPS (items 15-19).

Results

The evaluation of the video recordings of the hand movements reveals that both patients (SCHIZ) and healthy controls (CONTR) performed the task according to the instructions. Those participants who did not perform correctly (e.g., interrupt actions) were excluded from further analysis, which was the case for two patients who were not capable to perform the task inside the scanner and one who did not complete the data acquisition.

Functional MRI data

Differences in levels of brain activity in CONTR and SCHIZ

Significant differences between brain activity in CONTR and SCHIZ were found in the intentional condition (INT) by a group-by-condition interaction [$(D+_{CONTR} > D-_{CONTR}) > (D+_{SCHIZ} > D-_{SCHIZ})$] in the right IFG (pars opercularis) at [42 11 31] (cluster size 37 voxel, P= .015 FWE corr. on cluster level; ROI-mask comprised right IFG, right pSTS, and left putamen) (Figure 2A). Contrast estimates for the differently activated cluster indicated more activation for D+ in contrast to D- in the control group and the opposite activation pattern (D->D+) in the patient group in the INT condition (see Figure 2B). No such effect was found for the nINT condition. This fact was addressed by analyzing interactions over both condi-

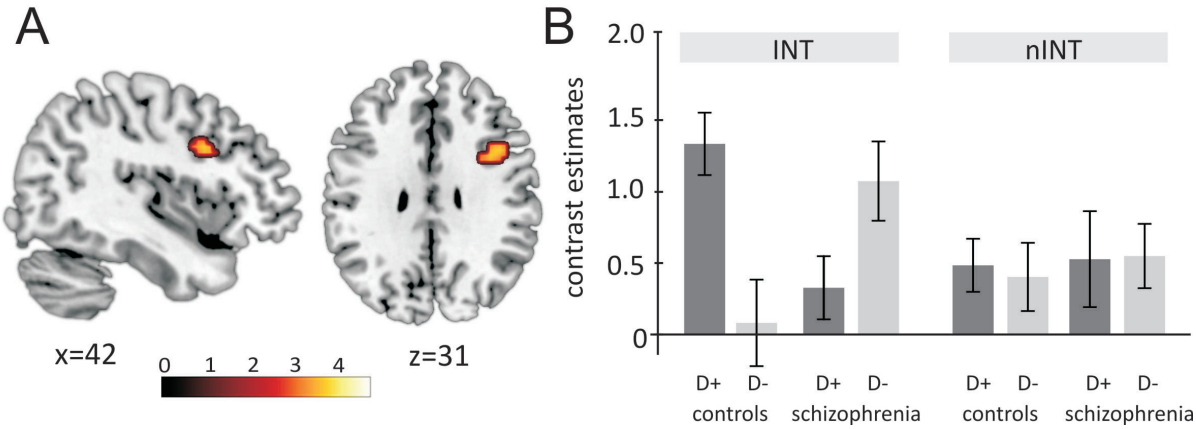

Figure 2. Activated cluster of the interaction between group and condition *[(D+ $_{CONTR}$ >D- $_{CONTR}$) > (D+$_{SCHIZ}$ > D- $_{SCHIZ}$)]. The bars in **B** show mean contrast estimates extracted from the IFG cluster shown in **A** at [42 11 31] (P<.001 unc. for illustration purposes) separated for the intentional (INT) and non-intentional (nINT) condition. Error bars indicate the standard error of the mean. The color bar shows the corresponding z-value.*

tions (INT versus nINT) (i.e., (D+ $INT_{CONTR>SCHIZ}$ > D- $INT_{CONTR>SCHIZ}$)>(D+ $nINT_{CONTR>SCHIZ}$>D- $nINT_{CONTR>SCHIZ}$)), which revealed significant differences within the aforementioned IFG cluster (at [36 8 31], p=0.04 FWE cluster corr., 12 vox., same ROIs).

PPI and seed voxel connectivity

PPI and seed voxel connectivity analysis was performed from the IFG seed at [42 11 31] revealed by the interaction analysis (see above). The task-related PPI analysis indicated significantly reduced connectivity for D+ versus D- from the right IFG to a large cluster with peak activation in the medial orbitofrontal gyrus (OFC, [9 50 -2], [-12 47 1], 164 vox.) in SCHIZ compared to CONTR (Figure 3, supplementary Table 2). Additionally, SCHIZ showed significantly decreased task-unrelated seed voxel connectivity between IFG and a cluster in the left putamen [-18 8 4] (73 vox.) and a cluster in the left insula [-33 -25 13] (131 vox.). No differences in connectivity of the IFG were found for SCHIZ>CONTR.

To evaluate a possible relation of the altered connectivity pattern between IFG and medial OFC with ego-disturbance, we performed a correlation analysis of the first eigenvariate from the latter bilateral cluster and the individual amount of ego-disturbance (determined using SAPS). We found that the activation in the right OFC in response to D+ is significantly correlated with the sum of symptom ratings in patients (Spearman's rho r_s=.623, p=.01). We observed the same trend for the left hemisphere (r_s=.476, p=.06).

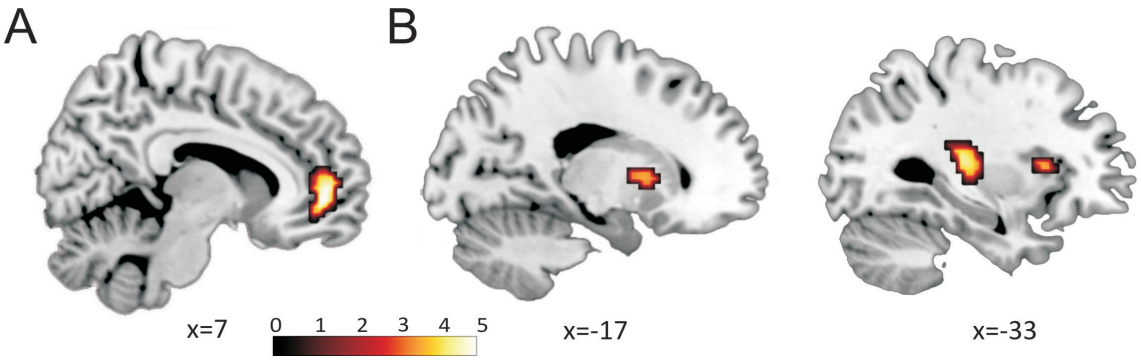

Figure 3. Functional dysconnectivity in SCHIZ, compared to CONTR. *The statistical parametric map shows regions with significantly decreased connectivity in SCHIZ with IFG time series. The orbitofrontal cluster in **A** represents the significant group PPI effect differences [(D+$_{CONTR}$>D-$_{CONTR}$) > (D+$_{SCHIZ}$>D-$_{SCHIZ}$)] found at a threshold of P < .05 FWE cluster corr. (whole-brain). The clusters in the left putamen and left insula in **B** reflect the significant group differences of the task-unrelated seed-voxel connectivity (CONTR>SCHIZ) found at P < .05 FWE cluster corr. (with ROI of insula, precentral gyrus, supplementary motor area, putamen, postcentral gyrus). The color bar shows the corresponding z-value.*

Discussion

Task activation analysis

We found a difference in the neural activation between patients with schizophrenia and healthy controls in one of our three regions of interest, that is in the IFG. This region is movement-sensitive and exhibits motor functions involved in complex hand movements (Binkofski and Buccino, 2004). The result has been exclusively triggered by the intentional movements, during which healthy participants showed activation if feedback was delayed while patients with schizophrenia showed the opposite pattern. The fact that we found this activation pattern in the IFG only for intentional movements might be explained by its increased recruitment when watching intentional hand-object interaction, rather than hand movements without intentions (see meta-analysis by Grosbras et al., 2012). In an earlier experiment (Leube et al., 2003b), IFG activation was associated with the detection of a harsh mismatch between one's own movement that stopped and a visual feedback that showed an ongoing movement.

In line with our finding, the dorsolateral prefrontal cortex, including IFG, has been associated with the sense of agency (David et al., 2008) or "other" processing (Farrer et al., 2004), detection of visual-motor incongruence (Schnell et al., 2008), successful monitoring of own or someone else's speech (Kumari et al., 2010), and sensory mismatch processing (Yomogida et al., 2010). Furthermore, our data in healthy controls are consistent with those of Macuga and Frey (2011) who showed that the right IFG responded differentially during live visual feedback of own repetitive hand movements versus perceptually similar, pre-recorded videos. The authors suggest that the IFG distinguishes between self and other by detecting subtle spatio-temporal differences between predicted and actual sensory feedback. We provide support for this suggestion by showing that the right IFG responds differently when the own feedback is temporally delayed and moreover extend this assumption by showing that time characteristics play a specific role for intentional rather than unintentional movements.

Derived from its response characteristics in our study, we suggest that the IFG is concerned with the efference mechanism showing lower (or suppressed) activation during "own" time-congruent feedback and increased activation while watching incongruent feedback, a situation when expectations of feedback were violated. The IFG is attenuated when incoming afference feedback signals are in line with the predicted time-course; putatively before it has received an efference copy from higher order motor cortices in order to filter expected, self-produced sensory information. Comparable results were found in studies in which externally tactile stimulation of the hand elicited greater activation in the bilateral secondary somatosensory cortex, than does self-produced stimulation (Blakemore et al., 1998).

In patients, the response pattern of the IFG is opposite to that of the controls, with an increased response during watching own time-congruent feedback. This is in line with other experiments demonstrating that in patients with schizophrenia, sensations following self-generated movements were not properly attenuated (e.g., Blakemore et al., 2000; Shergill et al., 2005). Moreover, a possible explanation for this activation pattern could be that the corollary discharge is temporally delayed in patients. Therefore the IFG is reached too late to suppress the sensory-evoked activity. This leads to the assumption that the experimental induced delayed feedback (+200 ms) compensates the temporal delay of suppression, and as a result the actual sensory feedback matches the expected feedback again. This could also explain findings of an earlier study in which patients were more likely to perceive a delay in visual feedback when, in fact, there was no delay when watching one's hand moving (Leube et al., 2010). Besides well known general impaired predictive timing in individuals with schizophrenia (e.g., Turgeon et al., 2012), experimental evidence for a normalization of neural suppressions by introducing a 50 ms delay to

self-generated auditory stimuli already exists, arguing that abnormalities in fasciculi connecting the frontal lobe with the rest of the brain result in a connectivity deficit introducing conduction delays in corollary discharges at the sensory cortex in schizophrenia (Whitford et al., 2011;2012).

The fact that the processing of intentional movements is affected in the IFG by temporal delays in particular may contribute to the assumption that the sense of agency could be influenced by the participant's intentions (Synofzik et al., 2008; Synofzik et al., 2009) and may account for over-attribution of temporal causality only during intentional action found in schizophrenia (Maeda et al., 2012)

Interestingly, the observed activation pattern corresponds to that found in other studies for the inferior parietal lobule (IPL), a likely candidate for a comparator. High activity in this region normally implies that another agent is acting (Ruby and Decety, 2001, Decety et al., 2002, Farrer and Frith, 2002) whereas in the case of patients with schizophrenia high activity implies a self-generated action. Similar to the IPL, the right IFG is embedded in the larger framework of the 'simulation coding system' and part of its putative neural substrate, i.e. the mirror neuron system (MNS; e.g., Carr et al., 2003; Rizzolatti and Fabbri-Destro, 2008; Rizzolatti and Craighero, 2004) (IFG: Kilner et al., 2009, Cattaneo et al., 2011). This network is active during both action production and observation of a similar action performed by another actor (Mukamel et al., 2010) - especially when goal-directed hand-object-interactions are involved (Gallese et al., 1996; Iacoboni et al., 2005), as it is the case in the intentional condition of the present study. The network provides a motor-based understanding of an observed motor act's goal performed by another individual through a mechanism that matches the motor act with an act in the observer's repertoire that has the same goal (Rizzolatti and Sinigaglia, 2010). When the processing of self and other share representations, there is a need for an additional mechanism realizing the disentangling of oneself or someone else as the agent (see Sebanz and Frith, 2004). To date, it is unclear which mechanisms accomplish this, but it has been argued that the matching mechanism addressed here could play a role (David et al., 2008; Leube et al., 2012). We give further support for this suggestion by demonstrating that the MNS-associated IFG (BA 44) differentiates between own time-congruent and temporal delayed feedback of intentional grasp-movements and therefore could manage a putative control mechanism. Furthermore, we suggest that this mismatch detection system is disturbed in schizophrenia on the level of the IFG and therefore may contribute to misattributions of agency and delusions of influence in schizophrenia.

Task-related and unrelated functional connectivity analysis

Using a PPI analysis we demonstrated that the functional connection between right IFG and a region of the orbitofrontal cortex (OFC) is significantly decreased in patients with schizophrenia compared to controls while processing own goal directed grasp-movements with delayed visual feedback. Differently from general connectivity reductions of the prefrontal cortex that are most frequently reported in schizophrenia (see Pettersson-Yeo et al., 2011) this dysconnection is specific for the condition with delayed feedback (D+ versus D-). Taken together with this finding, the demonstrated relation between the activity in the OFC (in response to delayed feedback) and ego-disturbance in patients suggests that this region is particularly involved in an altered processing of the mismatch between current performed action and time-incongruent feedback in patients with passivity symptoms. One can hypothesize that communication necessary for accurate transmission of signals to properly match planned action and received feedback is disturbed through the altered connection between IFG and OFC. This assumption is supported by the role of the OFC during agency judgments (Moll et al., 2007; Miele et al., 2011), in particular about the self (van der Meer et al., 2010). Furthermore, the OFC receives sensory feedback from inside and outside the body, e.g. somatosensory and visual information (data from monkeys: Carmichael and Price, 1995;

human: Kringelbach and Rolls, 2004), which could be provided for the aforementioned control mechanism in the IFG in healthy individuals. Using the seed voxel approach, we additionally found that - irrespective of the task - the functional connection between IFG to insula and putamen of the left hemisphere is decreased in schizophrenia compared to controls. Both regions have been constantly reported in the context of action monitoring and as crucial in agency processes (insula: e.g., Karnath et al. 2005; Brass and Haggard, 2007; Klein et al., 2013, Nahab et al., 2011, Tsakiris et al., 2010; putamen: e.g., Blakemore et al., 2003; Leube et al., 2003a, 2010). Furthermore, in a prior study by Leube et al., (2003a) in which a comparable paradigm was used, the putamen as part of the basal ganglia and key region of motor-control (Turner and Desmurget, 2010) was negatively correlated with the temporal delay. The authors hypothesized that reduced putamen activity reflects a dysfunctional generation of motor predictions about the time at which the visual consequences of movements should occur (Leube et al., 2003a; 2010). The results of our fMRI study extend these findings by showing that reduced connectivity between the putamen and IFG may lead to an inaccurate transmission of motor predictions and consequently to missing attenuation of the IFG during perception of time-congruent visual feedback in patients with schizophrenia. It has been mentioned before that frontal functional dysconnectivity in schizophrenia affects corollary discharge and consequently leads to a breakdown in self-monitoring (Stephan et al., 2009). Imprecise predictions of one's own actions further result in misattributions of agency in schizophrenia (Synofzik et al., 2010).

Something similar may apply to the insula, which has been suggested to play a role while distinguishing self-associated and self-attributed sensory stimuli and accomplishing interoceptive awareness (Wylie and Tregellas, 2010; van der Meer et al., 2010), which in turn is important for judgments about 'self' versus 'non-self' (Damasio, 2003; Devue et al., 2007; Kircher et al., 2001). Furthermore, greater insula activation has been found for self- versus other-agency attribution (Farrer and Frith, 2002; Farrer et al., 2003). Therefore, its insufficient functional connection to the IFG in patients with schizophrenia observed in the present study could reflect missing transmission of necessary interoceptive feedback signals, normally used to match with motor predictions within the IFG.

Conclusions

Taken together, we could show that due to its response characteristic (i.e., sensitivity for temporal delayed feedback of own intentional grasp-movements versus time-congruent feedback) the right IFG is a potential candidate for a comparator within the efference copy model in healthy participants. Furthermore, the IFG could solve the problem within the MNS – that is self and other share neural representations. Due to IFG's sensitivity to sensory mismatch, a distinction on the basis of temporal deviations (here shown in a subtle dimension of 200 ms) of received feedback remains possible. Moreover, we suggest that the IFG is the neural correlate of the failure of the efference mechanism in schizophrenia due to its deficits during sensory mismatch detection that could explain misattributions of agency and consequently delusions of influence that arise in schizophrenia. This idea is supported by our findings related to the connectivity analyses, suggesting that the transmissions of afferent and reafferent information from the OFC and interoceptive information from the insula, as well as putative motor predictions for corollary discharge from the putamen to the IFG may be decreased in schizophrenia. This defective exchange of signals might influence the integration within the matching mechanism and this in turn might cause self-monitoring deficits in patients, which contribute to the psychopathology of schizophrenic disorders (see Farrer and Franck, 2007 for a review). Moreover, in accordance with the correlation between the OFC activity and passivity symptom-ratings, these findings highlight a specific role of this network for the formation of ego-disturbances.

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References

American Psychiatric Association. (1994). Diagnostic and Statistical Manual of Mental Disorders. Washington DC: American Psychiatric Association.

Andreasen, N. C. (1983). Scale for the Assessment of Negative Symptoms (SANS). Iowa City, IA : University of Iowa.

Andreasen, N. C. (1984). Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA : University of Iowa.

Andreasen, N. C., & Olsen, S. (1982). Negative v positive schizophrenia. Definition and validation. Archives of general psychiatry, 39, 789–94.

Bedenbender, J., Paulus, F. M., Krach, S., Pyka, M., Sommer, J., et al. (2011). Functional connectivity analyses in imaging genetics: considerations on methods and data interpretation. (Y. He, Ed.). PloS one, 6, e26354.

Binkofski, F., & Buccino, G. (2004). Motor functions of the Broca's region. Brain and language, 89, 362–9.

Blakemore, S. J., Oakley, D. A., & Frith, C. D. (2003). Delusions of alien control in the normal brain. Neuropsychologia, 41, 1058–1067.

Blakemore, S. J., Smith, J., Steel, R., Johnstone, C. E., & Frith, C. D. (2000). The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. Psychological medicine, 30, 1131–9.

Blakemore, S. J., Wolpert, D. M., & Frith, C. D. (1998). Central cancellation of self-produced tickle sensation. Nature neuroscience, 1, 635–40.

Brass, M., & Haggard, P. (2007). To do or not to do: the neural signature of self-control. The Journal of neuroscience : the official journal of the Society for Neuroscience, 27, 9141–5.

Brett, M., Johnsrude, I. S., & Owen, A. M. (2002). The problem of functional localization in the human brain. Nature reviews. Neuroscience, 3, 243–9.

Carmichael, S. T., & Price, J. L. (1995). Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. The Journal of comparative neurology, 363, 642–664.

Carr, L., Iacoboni, M., Dubeau, M.-C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proceedings of the National Academy of Sciences of the United States of America, 100, 5497–502.

Cattaneo, L., Barchiesi, G., Tabarelli, D., Arfeller, C., Sato, M., et al. (2011). One's motor performance predictably modulates the understanding of others' actions through adaptation of premotor visuo-motor neurons. Social cognitive and affective neuroscience, 6, 301–10.

Crapse, T. B., & Sommer, M. A. (2008). Corollary discharge across the animal kingdom. Nature reviews. Neuroscience, 9, 587–600.

Cullen, K. E. (2004). Sensory signals during active versus passive movement. Current opinion in neurobiology, 14, 698–706.

Damasio, A. (2003). Mental self: The person within. Nature, 423, 227.

David, N., Newen, A., & Vogeley, K. (2008). The "sense of agency" and its underlying cognitive and neural mechanisms. Consciousness and cognition, 17, 523–34.

Decety, J., Chaminade, T., Grèzes, J., & Meltzoff, A. N. (2002). A PET exploration of the neural mechanisms involved in reciprocal imitation. NeuroImage, 15, 265–72.

Devue, C., Collette, F., Balteau, E., Degueldre, C., Luxen, A., et al. (2007). Here I am: the cortical correlates of visual self-recognition. Brain research, 1143, 169–82.

Farrer, C., & Franck, N. (2007). Self-Monitoring in Schizophrenia. Current Psychiatry Reviews, 3, 9.

Farrer, C., Franck, N., Frith, C. D., Decety, J., Georgieff, N., et al. (2004). Neural correlates of action attribution in schizophrenia. Psychiatry research, 131, 31–44.

Farrer, C., Franck, N., Georgieff, N., Frith, C. D., Decety, J., et al. (2003). Modulating the experience of agency: a positron emission tomography study. NeuroImage, 18, 324–33.

Farrer, C., & Frith, C. D. (2002). Experiencing oneself vs another person as being the cause of an action: the neural correlates of the experience of agency. NeuroImage, 15, 596–603.

Feinberg, I. 1978. Efference copy and corollary discharge: implications for thinking and its disorders. Schizophrenia Bulletin 4, 636 – 640.

Fink, G. R. (1999). The neural consequences of conflict between intention and the senses. Brain, 122, 497–512.

Ford, J. M., & Mathalon, D. H. (2004). Electrophysiological evidence of corollary discharge dysfunction in schizophrenia during talking and thinking. Journal of psychiatric research, 38, 37–46.

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., et al. (1997). Psychophysiological and modulatory interactions in neuroimaging. NeuroImage, 6, 218–29.

Frith, C. D. (2005). The self in action: lessons from delusions of control. Consciousness and cognition, 14, 752–70.

Frith, C. D., Blakemore, S., & Wolpert, D. M. (2000). Explaining the symptoms of schizophrenia: abnormalities in the awareness of action. Brain research. Brain research reviews, 31, 357–63.

Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. Brain, 119, 593–609.

Grosbras, M.-H., Beaton, S., & Eickhoff, S. B. (2012). Brain regions involved in human movement perception: a quantitative voxel-based meta-analysis. Human brain mapping, 33, 431–54.

Haggard, P., Clark, S., & Kalogeras, J. (2002). Voluntary action and conscious awareness. Nature neuroscience, 5, 382–5.

Von Holst, E., & Mittelstaedt, H. (1950). Das Reafferenzprinzip. Die Naturwissenschaften, 37, 464–476.

Iacoboni, M. (2005). Neural mechanisms of imitation. Current opinion in neurobiology, 15, 632–7.

Jeannerod, M., & Pacherie, E. (2004). Agency, Simulation and Self-identification. Mind and Language, 19, 113–146.

Karnath, H.-O., Baier, B., & Nägele, T. (2005). Awareness of the functioning of one's own limbs mediated by the insular cortex? The Journal of neuroscience : the official journal of the Society for Neuroscience, 25, 7134–8.

Kilner, J. M., Neal, A., Weiskopf, N., Friston, K. J., & Frith, C. D. (2009). Evidence of mirror neurons in human inferior frontal gyrus. The Journal of neuroscience : the official journal of the Society for Neuroscience, 29, 10153–9.

Kircher, T. T. ., Senior, C., Phillips, M. L., Rabe-Hesketh, S., Benson, P. J., et al. (2001). Recognizing one's own face. Cognition, 78, B1–B15.

Klein, T. A., Ullsperger, M., & Danielmeier, C. (2013). Error awareness and the insula: links to neurological and psychiatric diseases. Frontiers in human neuroscience, 7, 14.

Kringelbach, M. L., & Rolls, E. T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Progress in neurobiology, 72, 341–72.

Kumari, V., Fannon, D., Ffytche, D. H., Raveendran, V., Antonova, E., et al. (2010). Functional MRI of verbal self-monitoring in schizophrenia: performance and illness-specific effects. Schizophrenia bulletin, 36, 740–55.

Lehrl, S., Triebig, G., & Fischer, B. (1995). Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. Acta Neurologica Scandinavica, 91, 335–345.

Leube, D. T., Knoblich, G., Erb, M., Grodd, W., Bartels, M., et al. (2003). The neural correlates of perceiving one's own movements. NeuroImage, 20, 2084–2090.

Leube, D. T., Knoblich, G., Erb, M., & Kircher, T. T. J. (2003). Observing one's hand become anarchic: an fMRI study of action identification. Consciousness and cognition, 12, 597–608.

Leube, D. T., Knoblich, G., Erb, M., Schlotterbeck, P., & Kircher, T. T. J. (2010). The neural basis of disturbed efference copy mechanism in patients with schizophrenia. Cognitive Neuroscience, 1, 111–117.

Leube, D. T., Straube, B., Green, A., Blümel, I., Prinz, S., et al. (2012). A possible brain network for representation of cooperative behavior and its implications for the psychopathology of schizophrenia. Neuropsychobiology, 66, 24–32.

Leube, D., Whitney, C., & Kircher, T. (2008). The neural correlates of ego-disturbances (passivity phenomena) and formal thought disorder in schizophrenia. European archives of psychiatry and clinical neuroscience, 258 Suppl, 22–7.

Lindner, A., Thier, P., Kircher, T. T. J., Haarmeier, T., & Leube, D. T. (2005). Disorders of agency in schizophrenia correlate with an inability to compensate for the sensory consequences of actions. Current biology : CB, 15, 1119–24.

Macuga, K. L., & Frey, S. H. (2011). Selective responses in right inferior frontal and supramarginal gyri differentiate between observed movements of oneself vs. another. Neuropsychologia, 49, 1202–7.

Maeda, T., Kato, M., Muramatsu, T., Iwashita, S., Mimura, M., et al. (2012). Aberrant sense of agency in patients with schizophrenia: forward and backward over-attribution of temporal causality during intentional action. Psychiatry research, 198, 1–6.

Van der Meer, L., Costafreda, S., Aleman, A., & David, A. S. (2010). Self-reflection and the brain: a theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. Neuroscience and biobehavioral reviews, 34, 935–46.

Miele, D. B., Wager, T. D., Mitchell, J. P., & Metcalfe, J. (2011). Dissociating neural correlates of action monitoring and metacognition of agency. Journal of cognitive neuroscience, 23, 3620–36.

Moll, J., De Oliveira-Souza, R., Garrido, G. J., Bramati, I. E., Caparelli-Daquer, E. M. A., et al. (2007). The self as a moral agent: linking the neural bases of social agency and moral sensitivity. Social neuroscience, 2, 336–52.

Mukamel, R., Ekstrom, A. D., Kaplan, J., Iacoboni, M., & Fried, I. (2010). Single-neuron responses in humans during execution and observation of actions. Current biology : CB, 20, 750–6.

Nahab, F. B., Kundu, P., Gallea, C., Kakareka, J., Pursley, R., et al. (2011). The neural processes underlying self-agency. Cerebral cortex (New York, N.Y. : 1991), 21, 48–55.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 9, 97–113.

Pettersson-Yeo, W., Allen, P., Benetti, S., McGuire, P., & Mechelli, A. (2011). Dysconnectivity in schizophrenia: where are we now? Neuroscience and biobehavioral reviews, 35, 1110–24.

Pynn, L. K., & Desouza, J. F. X. (2013). The function of efference copy signals: implications for symptoms of schizophrenia. Vision research, 76, 124–33.

Rizzolatti, G., & Craighero, L. (2004). The mirror-neuron system. Annual review of neuroscience, 27, 169–92.

Rizzolatti, G., & Fabbri-Destro, M. (2008). The mirror system and its role in social cognition. Current opinion in neurobiology, 18, 179–84.

Rizzolatti, G., & Sinigaglia, C. (2010). The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. Nature reviews. Neuroscience, 11, 264–74.

Ruby, P., & Decety, J. (2001). Effect of subjective perspective taking during simulation of action: a PET investigation of agency. Nature neuroscience, 4, 546–50.

Schnell, K., Heekeren, K., Daumann, J., Schnell, T., Schnitker, R., et al. (2008). Correlation of passivity symptoms and dysfunctional visuomotor action monitoring in psychosis. Brain : a journal of neurology, 131, 2783–97.

Sebanz, N., & Frith, C. D. (2004). Beyond simulation? Neural mechanisms for predicting the actions of others. Nature neuroscience, 7, 5–6.

Shergill, S. S., Samson, G., Bays, P. M., Frith, C. D., & Wolpert, D. M. (2005). Evidence for sensory prediction deficits in schizophrenia. The American journal of psychiatry, 162, 2384–6.

Sperry, R. W. (1950). Neural basis of the spontaneous optokinetic response produced by visual inversion. Journal of comparative and physiological psychology, 43, 482–9.

Stephan, K. E., Friston, K. J., & Frith, C. D. (2009). Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophrenia bulletin, 35, 509–27.

Synofzik, M., Thier, P., Leube, D. T., Schlotterbeck, P., & Lindner, A. (2010). Misattributions of agency in schizophrenia are based on imprecise predictions about the sensory consequences of one's actions. Brain : a journal of neurology, 133, 262–71.

Synofzik, M., Vosgerau, G., & Lindner, A. (2009). Me or not me--an optimal integration of agency cues? Consciousness and cognition, 18, 1065–8.

Synofzik, M., Vosgerau, G., & Newen, A. (2008). Beyond the comparator model: a multifactorial two-step account of agency. Consciousness and cognition, 17, 219–39.

Tsakiris, M., Longo, M. R., & Haggard, P. (2010). Having a body versus moving your body: neural signatures of agency and body-ownership. Neuropsychologia, 48, 2740–9.

Turgeon, M., Giersch, A., Delevoye-Turrell, Y., & Wing, A. M. (2012). Impaired predictive timing with spared time interval production in individual with schizophrenia. Psychiatry research, 197, 13–8.

Turner, R. S., & Desmurget, M. (2010). Basal ganglia contributions to motor control: a vigorous tutor. Current opinion in neurobiology, 20, 704–16.

Whitford, T. J., Ford, J. M., Mathalon, D. H., Kubicki, M., & Shenton, M. E. (2012). Schizophrenia, myelination, and delayed corollary discharges: a hypothesis. Schizophrenia bulletin, 38, 486–94.

Whitford, T. J., Mathalon, D. H., Shenton, M. E., Roach, B. J., Bammer, R., et al. (2011). Electrophysiological and diffusion tensor imaging evidence of delayed corollary discharges in patients with schizophrenia. Psychological medicine, 41, 959–69.

Wild, B., Erb, M., Lemke, N., Scholz, P., Bartels, M., et al. (2000). Video camera and light system for application in magnetic resonance scanners. Magnetic Resonance Imaging, 18, 893–896.

Wittchen, HU, Wunderlich, U, Gruschwitz, S, Zaudig, M. (1997). Strukturiertes Klinisches Interview für DSM-IV (SKID). Göttingen: Beltz-Test.

Wolpert, D., Ghahramani, Z., & Jordan, M. (1995). Are arm trajectories planned in kinematic or dynamic coordinates? An adaptation study. Experimental Brain Research, 103.

Wylie, K. P., & Tregellas, J. R. (2010). The role of the insula in schizophrenia. Schizophrenia research, 123, 93–104.

Yomogida, Y., Sugiura, M., Sassa, Y., Wakusawa, K., Sekiguchi, A., et al. (2010). The neural basis of agency: an fMRI study. NeuroImage, 50, 198–207.

Supplementary Material

This material supplements but does not replace the content of the peer-reviewed paper published in Psychiatry Research: Neuroimaging

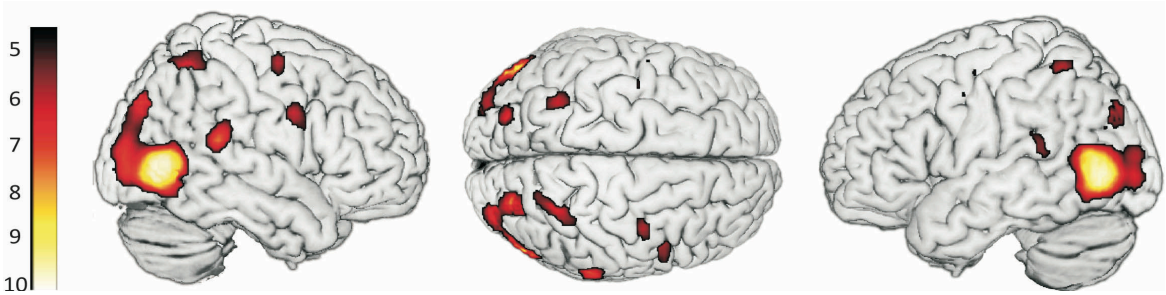

Figure 1.: Differential contrast of visual feedback (INT, nINT) versus static feedback baseline (ISI) in CONTR (INT+nINT>ISI). *Significant activated areas involved in visuomotor integration irrespective of delay length are shown in orange-red, e.g., frontal (notably the IFG), temporal (e.g., pSTS), temporooccipital, and sensorimotor brain areas. The color bar shows the corresponding z-value. P<.05 FWE corr; k=20.*

Table 1*. Neural activation in CONTR of all events vs. baseline irrespective of condition*

Area	MNI coordinates			Cluster size	z value	Cluster level p FWE corr.
	x	y	z			
Right Middle Temporal Gyrus	48	-61	4	993	>8.00	0.000
Right Superior Occipital Gyrus	27	-76	37		7.57	
Right Middle Occipital Gyrus	33	-88	7		6.95	
Left Middle Occipital Gyrus	-45	-70	4	770	>8.00	0.000
Left Inferior Occipital Gyrus	-27	-91	-2		6.29	
Left Middle Occipital Gyrus	-30	-91	10		5.95	
Right Inferior Parietal Lobule	30	-52	55	168	6.68	0.000
Right Superior Temporal Gyrus	63	-34	16	139	7.66	0.000
Right Inferior Frontal Gyrus p. Opercularis	48	5	31	113	6.37	0.000
Left Middle Occipital Gyrus	-24	-76	31	110	6.77	0.000
Left Inferior Parietal Lobule	-30	-52	55	73	6.14	0.000
Right Middle Frontal Gyrus	42	-4	58	46	6.08	0.001
Left Precentral Gyrus	-42	-7	55	24	4.90	0.003
	-54	-1	43			

Note. Activations are reported if P<.05 FWE corrected; cluster extent threshold (k)=20, n=16

Table 2. *Regions showing significantly lower task-related PPI functional connectivity and task-unrelated functional seed-voxel connectivity with the right IFG in SCHIZ compared to CONTR.*

Area	***MNI coordinates***			***Cluster size***	***z value***	***Cluster level P FWE corr.***
PPI connectivity [a]	x	y	z			
Right Mid Orbital Gyrus	9	50	-2	164	4.36	0.011
Left Mid Orbital Gyrus	-12	47	1		3.43	
Seed-voxel connectivity [b]						
Left Insula	-33	-25	13	131	4.41	0.008
Left Superior Temporal Gyrus	-39	-10	-8		3.85	
Left Insula	-39	-4	7		3.45	
Left Putamen	-18	8	4	73	3.65	0.032
Left Insula	-39	8	7		3.27	

P< .05 FWE cluster level corr.; k=20; nSCHIZ/nCONTR =16/16,
Note a. whole brain; b. ROI analysis

Verzeichnis der akademischen Lehrer

Meine akademischen Lehrer waren die Damen/Herren in Marburg:

Beck	Bölker	Exner
Galland	Hassel	Homberg
Jansen	Kircher	Kirchner
Klingenspor	Lachnit	Leube
Mörschel	Rebscher	Renkawitz-Pohl
Rösler	Schachtner	Schulze
Schwarting	Stengl	Weber

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Eigener Anteil an dieser Arbeit

Laut §8, Absatz 3 der Promotionsordnung der Philipps-Universität Marburg (Fassung vom 15.07.2009) müssen bei den Teilen der Dissertation, die aus gemeinsamer Forschungsarbeit entstanden sind, „die individuellen Leistungen des Doktoranden deutlich abgrenzbar und bewertbar sein“. Dies betrifft die Manuskripte #1-3, und wird im Folgenden detailliert erläutert.

Studie 1: Wahrnehmung Kooperativen Verhaltens bei Patienten mit Schizophrenie

- Hypothesengenerierung
- Auswahl und Implementierung des vorhandenen Stimulusmaterials in die fMRT Umgebung sowie Aufstellung des Studiendesigns
- Rekrutierung aller Probanden und Patienten
- Durchführung aller fMRT-Messungen, Interviews und Fragebogenerhebungen
- Auswertung, statistische Analyse und Interpretation aller Daten
- Anfertigung aller Abbildungen und Tabellen
- Anfertigung des Manuskriptes (Korrektur durch PD Dr. Leube, Dr. Straube und Prof. Dr. Kircher)

Eigener Anteil gesamt: 80%

Dieses Manuskript wurde in der vorliegenden Form im Journal *Social Neuroscience* zur Veröffentlichung akzeptiert:

Backasch, B., Straube, B., Pyka, M., Klöhn-Saghatolislam, F., Müller, M.J., Kircher, T.T.J., & Leube, D.T. (in press). Hyperintentionality during automatic perception of naturalistic cooperative behavior in patients with schizophrenia.

Studie 2: Integrität des Spiegelneuronensystems bei Patienten mit Schizophrenie

- Idee und Hypothesengenerierung
- Entwicklung des Stimulusmaterials und Implementierung in die fMRT Umgebung sowie Aufstellung des Studiendesigns
- Rekrutierung aller Probanden und Patienten
- Durchführung aller fMRT-Messungen, Interviews und Fragebogenerhebungen
- Auswertung, statistische Analyse und Interpretation aller Daten
- Anfertigung aller Abbildungen und Tabellen
- Anfertigung des Manuskriptes (Korrektur durch PD Dr. Leube, Prof. Dr. Jansen und Prof. Dr. Kircher)

Eigener Anteil gesamt: 80%

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Backasch, B., Jansen, A., Klöhn-Saghatolislam, F., Müller, M.J., Kircher, T.T.J., & Leube, D.T. (submitted). Impaired action information processing within the mirror neuron network in patients with schizophrenia.

Studie 3: Wahrnehmung verzögerter Eigenhandlungen

- Implementierung der von Dr. Erb bereitgestellten Software in abgewandelter Form in die fMRT Umgebung mit Hilfe von Dr. Sommer sowie Aufstellung des Studiendesigns
- Hypothesengenerierung
- Auswahl der repetitiven zielgerichteten Handbewegungen

- Rekrutierung aller Probanden und Patienten
- Durchführung aller fMRT-Messungen, Interviews und Fragebogenerhebungen
- Auswertung und statistische Analyse aller Daten
- Interpretation der Daten
- Anfertigung aller Abbildungen und Tabellen
- Anfertigung des Manuskriptes (Korrektur durch Prof. Dr. Jansen & Prof. Dr. Kircher)

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Backasch, B., Sommer, J., Klöhn-Saghatolislam, F., Müller, M.J., Kircher, T.T.J., & Leube, D.T. (submitted). Dysconnectivity of the inferior frontal gyrus: implications for an impaired self-other distinction in patients with schizophrenia.